Cochrane Library

Cochrane Database of Systematic Reviews

Probiotics for treating acute infectious diarrhoea (Review)

Collinson S, Deans A, Padua-Zamora A, Gregorio GV, Li C, Dans LF, Allen SJ

Collinson S, Deans A, Padua-Zamora A, Gregorio GV, Li C, Dans LF, Allen SJ.
Probiotics for treating acute infectious diarrhoea.
Cochrane Database of Systematic Reviews 2020, Issue 12. Art. No.: CD003048.
DOI: 10.1002/14651858.CD003048.pub4.

www.cochranelibrary.com

TABLE OF CONTENTS

[Intervention Review]

Probiotics for treating acute infectious diarrhoea

Shelui Collinson[1], Andrew Deans[2], April Padua-Zamora[3], Germana V Gregorio[3], Chao Li[4], Leonila F Dans[3], Stephen J Allen[1]

[1]Department of Clinical Sciences, Liverpool School of Tropical Medicine, Liverpool, UK. [2]Urgent Care, Team Medical, Paraparaumu, New Zealand. [3]Department of Pediatrics, University of the Philippines Manila College of Medicine-Philippine General Hospital, Manila, Philippines. [4]Tropical Clinical Trials Unit, Liverpool School of Tropical Medicine, Liverpool, UK

Contact: Stephen J Allen, Stephen.Allen@lstmed.ac.uk.

Editorial group: Cochrane Infectious Diseases Group.
Publication status and date: New search for studies and content updated (conclusions changed), published in Issue 12, 2020.

Citation: Collinson S, Deans A, Padua-Zamora A, Gregorio GV, Li C, Dans LF, Allen SJ. Probiotics for treating acute infectious diarrhoea. *Cochrane Database of Systematic Reviews* 2020, Issue 12. Art. No.: CD003048. DOI: 10.1002/14651858.CD003048.pub4.

ABSTRACT

Background

Probiotics may be effective in reducing the duration of acute infectious diarrhoea.

Objectives

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

Search methods

We searched the trials register of the Cochrane Infectious Diseases Group, MEDLINE, and Embase from inception to 17 December 2019, as well as the Cochrane Controlled Trials Register (Issue 12, 2019), in the Cochrane Library, and reference lists from studies and reviews. We included additional studies identified during external review.

Selection criteria

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

Data collection and analysis

Two review authors independently applied inclusion criteria, assessed risk of bias, and extracted data. Primary outcomes were measures of diarrhoea duration (diarrhoea lasting ≥ 48 hours; duration of diarrhoea). Secondary outcomes were number of people hospitalized in community studies, duration of hospitalization in inpatient studies, diarrhoea lasting ≥ 14 days, and adverse events.

Main results

We included 82 studies with a total of 12,127 participants. These studies included 11,526 children (age < 18 years) and 412 adults (three studies recruited 189 adults and children but did not specify numbers in each age group). No cluster-randomized trials were included. Studies varied in the definitions used for "acute diarrhoea" and "end of the diarrhoeal illness" and in the probiotic(s) tested. A total of 53 trials were undertaken in countries where both child and adult mortality was low or very low, and 26 where either child or adult mortality was high.

Risk of bias was high or unclear in many studies, and there was marked statistical heterogeneity when findings for the primary outcomes were pooled in meta-analysis. Effect size was similar in the sensitivity analysis and marked heterogeneity persisted. Publication bias was demonstrated from funnel plots for the main outcomes.

In our main analysis of the primary outcomes in studies at low risk for all indices of risk of bias, no difference was detected between probiotic and control groups for the risk of diarrhoea lasting ≥ 48 hours (risk ratio (RR) 1.00, 95% confidence interval (CI) 0.91 to 1.09; 2 trials, 1770 participants; moderate-certainty evidence); or for duration of diarrhoea (mean difference (MD) 8.64 hours shorter, 95% CI 29.4 hours shorter to 12.1 hours longer; 6 trials, 3058 participants; very low-certainty evidence).

Effect size was similar and marked heterogeneity persisted in pre-specified subgroup analyses of the primary outcomes that included all studies. These included analyses limited to the probiotics *Lactobacillus rhamnosus* GG and *Saccharomyces boulardii*. In six trials (433 participants) of *Lactobacillus reuteri,* there was consistency amongst findings (I^2 = 0%), but risk of bias was present in all included studies. Heterogeneity also was not explained by types of participants (age, nutritional/socioeconomic status captured by mortality stratum, region of the world where studies were undertaken), diarrhoea in children caused by rotavirus, exposure to antibiotics, and the few studies of children who were also treated with zinc. In addition, there were no clear differences in effect size for the primary outcomes in post hoc analyses according to decade of publication of studies and whether or not trials had been registered.

For other outcomes, the duration of hospitalization in inpatient studies on average was shorter in probiotic groups than in control groups but there was marked heterogeneity between studies (I^2 = 96%; MD -18.03 hours, 95% CI -27.28 to -8.78, random-effects model: 24 trials, 4056 participants). No differences were detected between probiotic and control groups in the number of people with diarrhoea lasting ≥ 14 days (RR 0.49, 95% CI 0.16 to 1.53; 9 studies, 2928 participants) or in risk of hospitalization in community studies (RR 1.26, 95% CI 0.84 to 1.89; 6 studies, 2283 participants).

No serious adverse events were attributed to probiotics.

Authors' conclusions

Probiotics probably make little or no difference to the number of people who have diarrhoea lasting 48 hours or longer, and we are uncertain whether probiotics reduce the duration of diarrhoea. This analysis is based on large trials with low risk of bias.

PLAIN LANGUAGE SUMMARY

Do probiotics help to treat acute infectious diarrhoea?

What is the aim of this review?

Acute infectious diarrhoea is a major global disease that particularly affects people in low- and middle-income countries. We wanted to know if taking probiotics is helpful in shortening the time taken for symptoms to resolve. We searched for studies that looked at the use of probiotics in people with acute diarrhoea. We looked for studies in which the treatments people received were decided randomly; these usually give reliable evidence.

Key messages

Probiotics may not affect how long acute diarrhoea lasts. We do not know if they can shorten the time to recovery from diarrhoea. We need reliable evidence from further studies to determine whether probiotics help treat acute infectious diarrhoea.

What was studied in the review?

”Diarrhoea” is the name for frequent bowel movements or the passing of unusually soft or watery faeces. Infections of the gut by bacteria, viruses, or parasites cause acute diarrhoea and are most often spread through water contaminated with faeces. Acute diarrhoea usually improves within a few days. However, in severe acute diarrhoea, water, salts, and nutrients that may be lost from the body are substantial, causing dehydration and even death. Treatments for acute diarrhoea aim to prevent or reverse dehydration, speed up recovery time, and shorten the time that a person may pass the infection to others.

Probiotics are live bacteria and yeasts that are thought to restore the natural balance of bacteria in the gut (intestines) when this has been disrupted by illness or treatment. Probiotics are often described as "good" or "friendly" bacteria; they may be present in yoghurts or taken as food supplements. In acute infectious diarrhoea, probiotics may act against the harmful microbes that are causing diarrhoea, help the gut to fight them, or reduce inflammation and damage to the gut.

What are the main results of the review?

We found 82 studies in 12,127 people (mostly children) with acute diarrhoea. Only 26 studies took place in countries that had high numbers of deaths (of any cause) among adults and children.

These studies compared the effects of different types of probiotics with no additional treatment or with a placebo (dummy) treatment. We were interested in:

• how many people had diarrhoea longer than 48 hours; and
• how long, on average, the symptoms of diarrhoea lasted.

There were many differences in the ways these studies were designed and carried out. Studies used different definitions of "acute diarrhoea" and "the end of diarrhoea symptoms," and they tested many different probiotics. Therefore, we could not include the results of all studies in our analysis.

We did not detect a difference between taking a probiotic and taking a placebo or no additional treatment in the number of children who had diarrhoea longer than 48 hours (two studies in high-income countries; 1770 children). We are uncertain whether taking probiotics affects the length of time that the symptoms of diarrhoea last (six studies; 3058 people). These findings were not affected by age, nutritional and socioeconomic status, region, or rotavirus infection of participants, nor by whether they were taking antibiotic medicines or zinc supplements.

Taking probiotics may not have affected:

• how many people had diarrhoea longer than 14 days (nine studies; 2928 people); or
• how many people were admitted to hospital with diarrhoea (six studies; 2283 people).

It was unclear whether taking probiotics shortened the time spent in hospital compared with taking a placebo or no additional treatment (24 studies; 4056 people). Few studies reported on any unwanted effects of probiotics; no serious unwanted effects were reported among people who took probiotics.

How reliable are these results?

Previous published editions of this review drew conclusions from the many small studies in this field and indicated an effect.

This new analysis shows that in this topic there is publication bias, with small studies demonstrating a positive effect more likely to be published, which skews the results. This fresh analysis takes this into account.

How up-to-date is this review?

We included evidence published up to 17 December 2019.

SUMMARY OF FINDINGS

Summary of findings 1. Summary of findings table 1

Probiotic compared to placebo for treating acute infectious diarrhoea (analysis limited to studies at low risk of bias)

Patient or population: children and adults with acute infectious diarrhoea
Setting: trials undertaken in health facilities and/or in the community in any country
Intervention: probiotic
Comparison: placebo or no probiotic/standard care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with probiotic				
Diarrhoea lasting ≥ 48 hours	536 per 1000	536 per 1000 (488 to 584)	RR 1.00 (0.91 to 1.09)	1770 (2 RCTs)	⊕⊕⊕⊖ MODERATE[a] Due to indirectness	Probiotics probably make little or no difference to the number of people who have diarrhoea lasting 48 hours or longer
Mean duration of diarrhoea (hours)	-	MD 8.64 hours lower (29.38 lower to 12.1 higher)	-	3058 (6 RCTs)	⊕⊖⊖⊖ VERY LOW[b,c] Due to imprecision and inconsistency	We are uncertain whether or not probiotics reduce the duration of diarrhoea

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; RCT: randomized controlled trial; RR: risk ratio.

GRADE Working Group grades of evidence.
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded by 1 for indirectness. Both trials conducted in high-income countries and evaluating two probiotics.
[b]Downgraded by 1 for imprecision. 95% confidence interval for the pooled estimate of probiotic effect includes a significant beneficial effect as well as the possibility that the duration of diarrhoea may be longer in people receiving probiotics.
[c]Downgraded by 2 for serious inconsistency. Probiotic effect varied markedly between trials, represented by an I^2 value of 97%.

BACKGROUND

Probiotics are recommended by some authorities for treatment of acute infectious diarrhoea, but the evidence base is limited. We updated our previous review (Allen 2010), to re-evaluate the evidence for their use.

Description of the condition

Diarrhoea is defined by the World Health Organization (WHO) as three or more loose or watery stools (taking the shape of the container) in a 24-hour period. Diarrhoea is classified as acute if the illness started less than 14 days previously, and as persistent if the episode has lasted 14 days or longer (Anonymous 1988). Normal infants who are exclusively breast-fed may pass loose, "pasty" stools frequently. For 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.

Although mortality due to diarrhoea fell by more than 30% between 2000 and 2015, diarrhoea accounted for 526,000 under five deaths in 2015 and was the second leading cause of death in children aged one to 59 months (Liu 2016a). Mortality rates amongst children have decreased despite low global usage of oral rehydration solution (ORS) and zinc for acute diarrhoea, with 43% of children globally receiving ORS between 2011 and 2016, and only an additional 9% receiving ORS plus zinc within the same period (UNICEF 2018). In industrialized countries, the trend is quite different, with deaths from infectious diarrhoea occurring mainly among the elderly (Savarino 1993). The incidence of childhood diarrhoea has seen a less promising decline (Das 2014). For children under five in low- and middle-income countries, diarrhoea incidence declined from 3.4 episodes per child per year to 2.9 episodes between 1990 and 2010 (Fischer-Walker 2012), and diarrhoea still accounts for a large proportion of hospital admissions (Das 2014).

More than 20 viruses, bacteria, and parasites are associated with acute diarrhoea (Gadewar 2005). The 2013 Global Enteric Multicenter Study (GEMS) and its subsequent reanalysis in 2016 identified six pathogen groups responsible for 77.8% of moderate to severe diarrhoeal episodes in children under five in countries in Africa and Asia: the bacteria *Shigella* spp, *Campylobacter* spp, and heat-stable enterotoxin-producing *Escherichia coli* (ST-ETEC); the viruses rotavirus and adenovirus 40/41; and the parasite *Cryptosporidium* spp (Kotloff 2013; Liu 2016b). Although *Shigella* spp was the dominant pathogen associated with dysentery, it also accounted for a large burden of watery diarrhoea (Liu 2016b). In an extension of the GEMS study, the spectrum of pathogens causing less severe diarrhoea in under five children was similar to that causing more severe episodes, with norovirus GII also identified as an important pathogen in children under one year (Kotloff 2019). 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 identification of the causative agent. WHO guidelines base treatment on clinical presentation (level of dehydration, malnutrition) and recommend additional management only for dysentery or suspected cholera (WHO 2005). Similarly, the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) recommends that, although some clinical features vary with different infectious diarrhoeal aetiologies, children with acute gastroenteritis do not routinely need to undergo investigation for the causative pathogen (Guarino 2014). Current WHO guidelines for children in low- and middle-income countries recommend that in addition to fluid therapy for children with acute non-bloody diarrhoea without severe dehydration, zinc supplementation should be given (WHO 2005).

Description of the intervention

The aims of treatment are to prevent or reverse dehydration, shorten the duration of illness (important for preventing progression to persistent diarrhoea, which is associated with adverse outcomes such as malnutrition), and reduce the period that a person is infectious. Available treatment options include oral and parenteral rehydration, zinc supplementation in children, antibiotics, adsorbents such as smectite, and probiotics.

For treatment of acute diarrhoea, Cochrane Reviews have examined ORS versus IV fluid (Hartling 2006), zinc supplementation (Lazzerini 2016), smectite (Pérez-Gaxiola 2018), rice-based oral rehydration solution (Fontaine 1998), polymer-based oral rehydration solution (Gregorio 2016), and antiemetics in children and adolescents (Fedorowicz 2011). This review examines probiotics.

A recent expert panel created by the International Scientific Association for Probiotics and Prebiotics (ISAPP) recommended retaining the Food and Agriculture Organization of the United Nations (FAO)/WHO definition for probiotics as “live microorganisms that, when administered in adequate amounts, confer a health benefit on the host” (Hill 2014). Common probiotics include the *Lactobacillus* and *Bifidobacterium* species of bacteria and the *Saccharomyces* species of yeast (Williams 2010).

How the intervention might work

Probiotics may improve infectious diarrhoea through multiple mechanisms including overt anti-pathogen effects (competition for nutrients and binding sites within the gut, producing substances such as bacteriocins and organic acids, and neutralizing bacterial toxins) and general effects such as stimulation of mucosal immune responses and reduction of intestinal inflammation and permeability (Guarner 2012; Halloran 2019; Surendran Nair 2017). Relevant to pooling results of different probiotic organisms, the ISAPP expert panel proposes that there may be "core" mechanisms, such as competitive exclusion of pathogens, that are common to many probiotics, whilst mechanisms such as immunological effects are likely to be species or strain specific. The panel concludes that a specific strain and dose must be defined before a health claim can be made for a probiotic (Hill 2014). Therefore, reliable identification of organisms at the strain level is necessary for clinical studies.

A 2011 systematic review on the safety of probiotics, based on their use in clinical trials, concluded that no increase in adverse outcomes was seen in probiotic groups (Hempel 2011). However, case studies suggest that particularly vulnerable patients may be at increased risk for adverse events, mostly gastrointestinal in nature, such as diarrhoea, vomiting, and constipation. An overview of specific populations studied in clinical trials identified one case of invasive disease in an immunocompromised patient and noted that better documentation on the safety of probiotics is needed (Doron 2015). Concerns regarding the safety of probiotics are especially

pertinent for highly vulnerable patients such as children receiving intensive care (Yelin 2019), as well as adults with severe acute pancreatitis (Besselink 2008).

Why it is important to do this review

Findings from the previous version of this Cochrane Review show that when probiotics were used, the mean duration of diarrhoea was shorter, and fewer children had diarrhoea lasting four days or longer. However, due to substantive heterogeneity of effect size between studies, evidence was insufficient to show a specific probiotic regimen as more effective than another (Allen 2010). Since the 2010 review, probiotics for the treatment of acute infectious diarrhoea have been evaluated in many more randomized controlled trials. However, in spite of this increased evidence base, recent systematic reviews have not identified a specific probiotic preparation for use in clinical practice. In a meta-analysis, probiotics reduced the duration of diarrhoea among children (weighted mean difference -0.67 days, 95% confidence interval (CI) -0.95 to -0.38; Salari 2012). In children from middle- and high-income countries, probiotics reduced diarrhoea duration by 14% (95% CI 3.8% to 24.2%) and stool frequency on day two by 13.1% (95% CI 0.8% to 25.3%; Applegate 2013). In both meta-analyses, evidence was insufficient to support a specific strain or regimen. Finally, two recent studies each recruited a large number of participants, potentially making a significant contribution to the evidence base (Freedman 2018a; Schnadower 2018).

The 4th Triennial Yale/Harvard Workshop on Probiotic Recommendations considered that there was a good level of evidence to recommend *Lactobacillus* GG, *Saccharomyces boulardii,* and *Lactobacillus reuteri* SD2112 for treatment of infectious childhood diarrhoea (Floch 2015). In contrast, the European Society of Paediatric Gastroenterology and Nutrition strongly recommended two strains - *Saccharomyces boulardii* and *Lactobacillus rhamnosus* GG - but with support of only low-quality evidence (Guarino 2015). Consistent with findings of the meta-analysis, a review of six guidelines on the use of probiotics in acute infectious diarrhoea in children highlighted marked variability in the recommendations for which probiotic strain and dose should be used in clinical practice (Guarino 2015). A recent clinical practice guideline based on a systematic review by the American Gastroenterological Association recommended that probiotics should not be used for treatment of acute infectious diarrhoea in children in the USA and Canada (conditional recommendation based on moderate-quality evidence; Su 2020).

We intended to assess whether the addition of trials undertaken since our previous review would reduce the statistical heterogeneity between studies, and whether there was greater evidence for any specific probiotic preparation. We also aimed to identify evidence gaps to ensure that further research informs the development of clinical guidelines.

OBJECTIVES

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

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials reporting the effects of probiotic(s) on acute infectious diarrhoea. To maximize the use of available data, we included participants of all ages and non-blinded (open) studies; however, to keep results as robust as possible, we did not include quasi-randomized and unpublished studies. We also did not include studies of probiotics in acute diarrhoea that did not report clinical outcomes (e.g. effect on rotavirus shedding in stools).

Types of participants

Adults and children with acute diarrhoea (duration < 14 days) that was proven or presumed to be caused by an infectious agent. To maximize the relevance of our findings for clinical practice, we included studies in which participants with acute diarrhoea had received antibiotics.

We excluded studies on diarrhoea known or thought to have other causes (e.g. studies on antibiotic-associated diarrhoea, studies of persistent diarrhoea).

Types of interventions

Interventions

Specific probiotic preparations (single strains and combinations of organisms).

Excluded was yogurt or other fermented foods in which specific probiotic organisms were not identified and killed probiotics.

Control

Placebo or no probiotic.

Intervention and control arms to be otherwise treated identically in relation to other treatments and drugs including zinc.

Types of outcome measures

In view of recent expert recommendations for a core outcome measurement set for acute diarrhoea in children (Karas 2016), we revised our outcomes to include the number of people hospitalized in community studies and the duration of hospitalization in inpatient studies as secondary outcomes. The Expert Panel also recommended degree of dehydration as an outcome measure. However, we did not include this outcome as it was rarely reported in trials included in our previous review (Allen 2010). We included diarrhoea lasting 14 days or longer to examine the proportion of patients progressing to persistent diarrhoea (Walker-Smith 1993). We included studies that reported one or more of the following primary or secondary outcomes.

Primary outcomes

- Diarrhoea lasting ≥ 48 hours
- Duration of diarrhoea

Secondary outcomes

- Numbers of people hospitalized in community studies
- Duration of hospitalization in inpatient studies

- Diarrhoea lasting ≥ 14 days

Adverse events

- Incidence of adverse events (serious and non-serious)

Search methods for identification of studies

Electronic searches

We attempted to identify all relevant studies regardless of language.

We searched the Cochrane Infectious Diseases Group's trials register using the following search terms: diarrhoea/; diarr $(tw); diarrhoea(tw); probiotic(tw); Lactobacill$(tw); Lactococc $(tw); Bifidobacter$(tw); Enterococc$(tw); Streptococc$(tw); Saccharomyces(tw). Full details of the methods of the Cochrane Infectious Diseases Group 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, using the following search terms: diarrhea/; diarr$(tw); diarhea(tw); probiotic(tw); Lactobacill$(tw); Lactococc$(tw); Bifidobacter$(tw); Enterococc$(tw); Streptococc $(tw); Saccharomyces(tw).

We searched MEDLINE and Embase using the search strategy defined by Cochrane (Clarke 2003), and we used the following search terms: diarrhea/; diarr$(tw); diarhea(tw); probiotic(tw); Lactobacill$(tw); Lactococc$(tw); Bifidobacter$(tw); Enterococc $(tw); Streptococc$(tw); Saccharomyces(tw).

The detailed search strategy is shown in Appendix 1.

Searching other resources

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

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

Data collection and analysis

SC, AD, and SA independently extracted data using standard forms. The number of participants recruited and the number for whom outcome data were reported were extracted and included in the Characteristics of included studies table.

In keeping with the ISAPP understanding of potential beneficial effects that are common to all probiotics (Hill 2014), the primary analysis pooled the findings from all eligible studies of probiotics in acute diarrhoea. We pooled data from studies that used comparable outcome measures. We reported the proportion of participants for whom outcome data were available in a 'Risk of bias' table for each study.

Selection of studies

Two review authors independently reviewed the titles of articles and, when 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 review authors were selected and the full article reviewed. Eligibility was assessed independently by these two people using a standard form and based on the information presented in the article. We planned to contact trial authors if eligibility was unclear. Discrepancies among reviewers' eligibility assessments were resolved by discussion. Trial reports were scrutinized to ensure that multiple publications from the same trial were included only once. We have listed excluded studies and the reasons for their exclusion in the Characteristics of excluded studies table.

Data extraction and management

Two review authors independently extracted data using standard forms and compared the results. Key data items were participants' characteristics (nutrition and hydration status), location (countries classified according to region and mortality stratum, reflecting the level of child and adult mortality; WHO 2001), aetiology and duration of diarrhoea, details of probiotic organism(s), management as inpatients versus outpatients; and the outcome measures listed above. The number of participants recruited and the number for whom outcome data were reported were extracted, and details of studies were entered into the Characteristics of included studies table.

For dichotomous outcomes, we extracted the number of participants experiencing the event and the total number of participants in each intervention group. For continuous outcomes, we extracted arithmetic means, standard deviations (SDs), and numbers of participants in each intervention group. We calculated mean and standard deviation from median and interquartile range for non-skewed data.

We also reported in the Characteristics of included studies table findings of trials that presented data that could not be included in pooled analyses (e.g. median and interquartile range (IQR) from skewed data) and outcomes other than primary and secondary outcomes.

Assessment of risk of bias in included studies

Two review authors independently assessed the risk of bias for each trial using the Cochrane 'Risk of bias' assessment tool (Higgins 2012). Risk of bias was based on primary outcomes and was categorized as low (adequate measures taken), high (inadequate measures taken), or unclear.

Risk of bias was assessed according to generation of allocation sequence, allocation concealment, blinding of participants, blinding of outcome assessment, loss to follow-up, and outcome reporting, and was recorded on a standard form.

We considered the generation of allocation sequence to be adequate if the study authors stated that they used a method resulting in unpredictable sequences (such as a random numbers table or list or computer-generated random numbers), unclear if a trial was stated to be randomized but no further information was provided, and inadequate when allocation could be related to

prognosis and therefore was at risk of selection bias (e.g. based on date of birth or date of admission to hospital).

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

We considered blinding of participants to be adequate when an identical placebo was used and recruitment to intervention or control arms was not known by the participant, unclear if methods of blinding were not described adequately, and inadequate when blinding was not used.

We considered blinding of outcome assessment to be adequate when recruitment to intervention or control arms was not known by the investigator, unclear if methods of blinding or assessors were not described adequately, and inadequate when blinding was not used or when study authors stated that unblinding had occurred.

We considered loss to follow-up to be adequate when study endpoints were reported in both intervention and control groups for 90% or more of participants enrolled at the beginning, inadequate when follow-up was less than 90% in either group, and unclear when the number of participants recruited at the beginning of the study and/or the number of participants who completed the study was not clear.

We considered outcome reporting to be adequate if all outcomes specified in the methods were reported fully in the results; inadequate if any intended outcomes were not reported or were not reported adequately, or if reported outcomes were not pre-specified; and unclear if it was not possible to judge based on the information given.

An independent person resolved disagreements regarding the assessment of risk of bias.

Measures of treatment effect

For the number of participants with diarrhoea lasting ≥ 48 hours, the number of people hospitalized in community studies, and the number with diarrhoea lasting 14 days or longer, we calculated a pooled estimate of the risk ratio (RR) among probiotic and non-probiotic groups. For duration of diarrhoea and duration of hospitalization in inpatient studies, we achieved a pooled estimate of treatment effect by calculating the weighted mean difference between groups.

Unit of analysis issues

For trials with multiple treatment groups but a single control arm (no additional treatment or placebo), we selected the treatment group that was most relevant to contributing to the evidence base for use of a specific probiotic preparation. All intervention groups are detailed in the Characteristics of included studies table.

Dealing with missing data

We performed intention-to-treat analysis of available case data with no imputation of missing values; we excluded data if reported only from a per-protocol analysis. In studies reporting continuous outcomes, if required, we calculated SDs from 95% CIs and standard errors.

Assessment of heterogeneity

We inspected forest plots to detect non-overlapping CIs, applied the Chi^2 test and implemented the I^2 statistic (with value ≥ 50%) to assess heterogeneity in findings.

Assessment of reporting biases

We inspected funnel plots and undertook statistical analysis for the primary outcomes to assess publication bias.

Data synthesis

For analysis according to the intention-to-treat principle using an available case analysis approach, we planned to use fixed-effect analysis unless there was significant heterogeneity ($P < 0.1$) for outcomes across studies assessed by the Chi^2 test, or when weighting was high for a small number of studies, in which case a random-effects model would be used.

Network meta-analysis (NMA)

NMA can compare the relative efficacy of probiotics that have been tested against placebo in different trials but without head-to-head comparisons. We planned to undertake NMA if we found sufficient trials and homogeneity in findings for specific probiotic preparations.

Certainty of the evidence

We assessed the certainty of evidence using the GRADE approach (Guyatt 2011). We rated the certainty of evidence for primary and secondary outcomes as:

- high: we are very confident that the true effect lies close to that of the estimate of the effect;
- moderate: we are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect;
- low: our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect; or
- very low: we have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

We downgraded the certainty of evidence if we noted significant risk of bias, imprecision, inconsistency, indirectness, and publication bias. We reported our overall assessment of the certainty of evidence for primary and secondary outcomes according to GRADE criteria in Summary of findings 1.

Subgroup analysis and investigation of heterogeneity

We undertook pre-planned subgroup analysis to explore the effects of clinical diversity on heterogeneity in results between studies and to re-assess the evidence base for specific probiotic preparations to better inform clinical practice. We also undertook subgroup analysis according to specific cause of diarrhoea when identified, age of participants, WHO region, mortality stratum to attempt to capture differences in major causes of diarrhoea, host characteristics such as nutritional/immune status, and exposure to infections according to availability of clean water and sanitation. Exposure to antibiotics may prolong diarrhoea duration or modify

the effect of the probiotic; therefore, subgroup analysis also considered antibiotic exposure. Finally, to date, no reviews have assessed the effects of probiotics for treatment of acute infectious diarrhoea when zinc is also provided; therefore, we performed a subgroup analysis of studies that also provided zinc.

We conducted pre-planned subgroup analyses for the primary outcomes according to the following variables when there were five or more studies in each subgroup.

- Strain(s) of probiotic organism.
- Major causes of diarrhoea as identified in children in the GEMS multi-country study in Africa and Asia: *Shigella spp*, *Campylobacter spp*, heat-stable enterotoxin-producing *E coli* (ST-ETEC), rotavirus, adenovirus 40/41, and *Cryptosporidium spp* (Liu 2016b), as well as any additional pathogens that were reported such as norovirus.
- Age (0 to 5 years, 6 to 17 years, 18 to 64 years, 65 years plus).
- Severity of diarrhoeal illness according to whether participants were managed as inpatients versus outpatients.
- Countries where studies were conducted classified according to WHO region (Africa (Afr), Americas (Amr), Eastern Mediterranean (Emr), Europe (Eur), South-East Asia (Sear), and Western Pacific (Wpr)) and country mortality stratum (A - very low child mortality, low adult mortality; B - low child mortality, low adult mortality; C - low child mortality, high adult mortality; D - high child mortality, high adult mortality; or E - high child mortality, very high adult mortality; WHO 2001).
- Exposure to antibiotics.
- Treatment of children with zinc.

We also conducted post hoc subgroup analysis according to publication decade, trial registration, and study setting to further investigate heterogeneity.

Sensitivity analysis

To investigate the robustness of findings, we conducted sensitivity analyses according to each of the six criteria of trial methodological quality (as part of the GRADE approach; GRADEpro GDT 2014) for the two primary outcomes. Sensitivity analysis was conducted in the subset of studies that were scored at low risk of bias for each of these criteria in turn and also in studies for which risk of bias was rated as low for all six parameters.

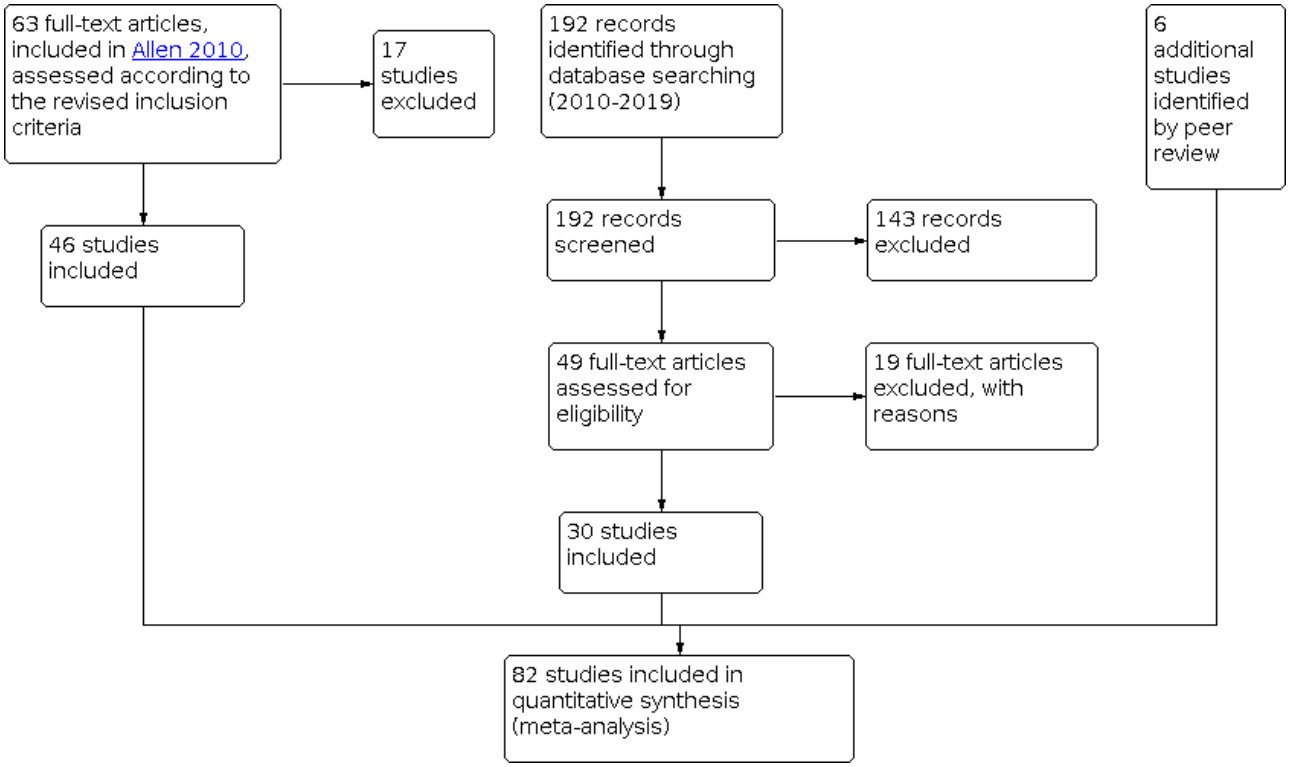
RESULTS

Description of studies

Results of the search

Our search identified 192 potentially relevant studies published since the 2010 review, 30 of which met the inclusion criteria. Of the 63 studies included in the 2010 review, 46 met the updated inclusion criteria. Six additional studies were identified through peer review (Figure 1). In total, 82 studies met the inclusion criteria (Characteristics of included studies). Eligibility regarding inclusion in this review was clear for all studies, and clarification from trial authors was not required. No studies were cluster-randomized.

Figure 1. Study flow diagram.



Eight studies were ongoing (search undertaken 17 December 2019; Characteristics of ongoing studies).

Included studies

Publication status

Of the 82 included studies, 17 were published in the 1980s and 1990s, 28 between 2000 and 2009, and 37 between 2010 and 2019.

Study locations

According to country mortality strata for children/adults (WHO 2001), 53 trials were undertaken in countries where both child and adult mortality was classified as low or very low, and 26 where either child or adult mortality was high. Two international studies recruited participants from countries crossing the mortality strata (Guandalini 2000; Jasinski 2002), and Ritchie 2010 was undertaken in Australia (very low child and low adult mortality) but recruited Aboriginal children who commonly had comorbidities such as pneumonia and malnutrition related to poverty and social disadvantage in the top end of the Northern Territory. Therefore, data from these three studies were not included in analysis according to country mortality strata. A total of 58 studies were conducted at a single centre; 22 recruited participants from 2 to 19 centres. The number of recruitment centres was unclear in two studies (D'Apuzzo 1982; Dinleyici 2015a).

Participants

The 82 selected studies recruited a total of 12,127 participants, including 11,526 children (age < 18 years) and 412 adults. In three studies (189 participants), the exact ages of participants were not clear or outcomes were not reported for children and adults separately (Bruno 1983; Simadibrata 2013; Wunderlich 1989). A total of 53 studies recruited inpatients, 11 recruited outpatients, and 14 recruited both inpatients and outpatients. It is unclear in four studies whether participants were inpatients or outpatients (Billoo 2006; Cetina-Sauri 1994; D'Apuzzo 1982; Kowalska-Duplaga 1999). Hydration status of participants was reported in 54 studies; 25 studies included participants with severe dehydration, 27 included participants with mild or moderate dehydration, 1 excluded participants with dehydration, and 1 presented median hydration scores but did not make clear whether any participants with severe dehydration were included.

Although all studies recruited participants with acute diarrhoea, the criteria for acute diarrhoea varied markedly among studies (see Characteristics of included studies). Criteria used for stool consistency included watery, loose(r), or liquid stools; semi-liquid or semi-watery; increased fluidity; mucus-y; and non-formed, taking the shape of the container or a combination of these terms. The minimum number of stools per day was specified in 58 studies; this ranged from one or more to five or more stools, with the most commonly used criteria being three or more (35 studies) and four or more (13 studies) stools in 24 hours. One study specified stool frequency as at least twice normal frequency (Kurugol 2005), and in another study, stool consistency was taken into account (Mao 2008). The maximum duration of diarrhoea at recruitment was specified in 43 studies and varied between 1 and 14 days. One study excluded children with chronic diarrhoea but did not specify the duration (Hochter 1990).

Criteria used for the end of the diarrhoeal episode were reported in 58 studies and varied markedly. The most common were last liquid, watery, or fluid stool and first normal stool. Many studies used various criteria based on stool frequency and consistency in a specified period (e.g. first formed stool if followed by two consecutive non-watery stools, 12 hours without evacuation; Mao 2008). Four studies also included the resolution of associated symptoms (e.g. fewer than two stools/d; formed, yellow/brown stools without mucus; no abdominal pain, vomiting, or fever for the whole day; D'Apuzzo 1982).

Twenty-seven studies were restricted to children with rotavirus diarrhoea or reported relevant outcomes for a subgroup of children with rotavirus diarrhoea (two study authors kindly provided this information on request: Freedman 2018a and Szymanski 2019). Twelve studies did not exclude participants with bloody diarrhoea, whereas 39 studies did exclude these participants. It is unclear whether participants with bloody diarrhoea were included in 31 studies. Thirty-seven studies excluded participants who had received antibiotic treatment before recruitment, 12 included participants who had received antibiotic treatment before recruitment, and this information was unclear in 33 studies.

No study specifically recruited or excluded travellers, and none identified any participants as suffering from travellers' diarrhoea. No study specifically recruited participants known to have HIV infection, and no study stated HIV positivity as an exclusion criterion, but many studies excluded participants with chronic illness or immunosuppression, or both. Seven studies recruited malnourished children only or included malnourished children. Forty studies excluded children with severe malnutrition; 10 of these also excluded children with moderate malnutrition.

Interventions

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

Fifty-seven studies tested a single organism, and 25 tested combinations of two to eight organisms. The organisms most commonly evaluated were *S boulardii* (21 studies), *L casei* strain GG (15 studies), and *L reuteri* spp (7 studies, 4 of which tested *L reuteri* DSM17938). Canani 2007 allocated children to one of five different probiotic regimens and compared outcomes with those of a single control group. For the purposes of this review, we selected the *L casei* GG group because several other studies tested this probiotic and we wanted to maximize the data available for meta-analysis. Similarly, Bhat 2018, Erdogan 2012, and Vidjeadevan 2018 allocated children to one of two different probiotic regimens and compared outcomes with those of a single control group. For the purposes of this review, we selected *S boulardii* as the most commonly studied organism across the other included studies.

Three studies compared different dosages (number of organisms) of the same probiotic with a single control (Basu 2009; Mao 2008; Shornikova 1997b). We selected the higher probiotic dose group for inclusion in meta-analysis but included results from the lower dose group in the Characteristics of included studies table. Freedman 2015 compared administration of a probiotic once daily and twice daily to use of a single control, presenting results separately and as a combined figure; the combined outcome was selected for inclusion in the review. Overall, 15 studies used a higher dose of

organisms (> 10^{10} colony-forming units (CFUs)/d), 39 used a lower dose (≤ 10^{10} CFUs/d), and the dose was unclear in 27 studies.

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

Fifty-four studies used a placebo in the no probiotic control group; the remaining studies treated participants according to usual clinical practice.

Risk of bias in included studies

Risk of bias varied considerably (see Characteristics of included studies; Figure 2). Forty-one (50.0%) studies were considered low risk for generation of the allocation sequence, 12 (14.6%) for concealment of allocation, 36 (43.9%) for blinding of participants and personnel, 30 (36.6%) for blinding of outcome assessment, 65 (79.3%) for loss to follow-up, and 71 (86.6%) for selective reporting (Figure 3). Seven studies (8.5%) were at low risk for all of the six methodological quality assessment parameters.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

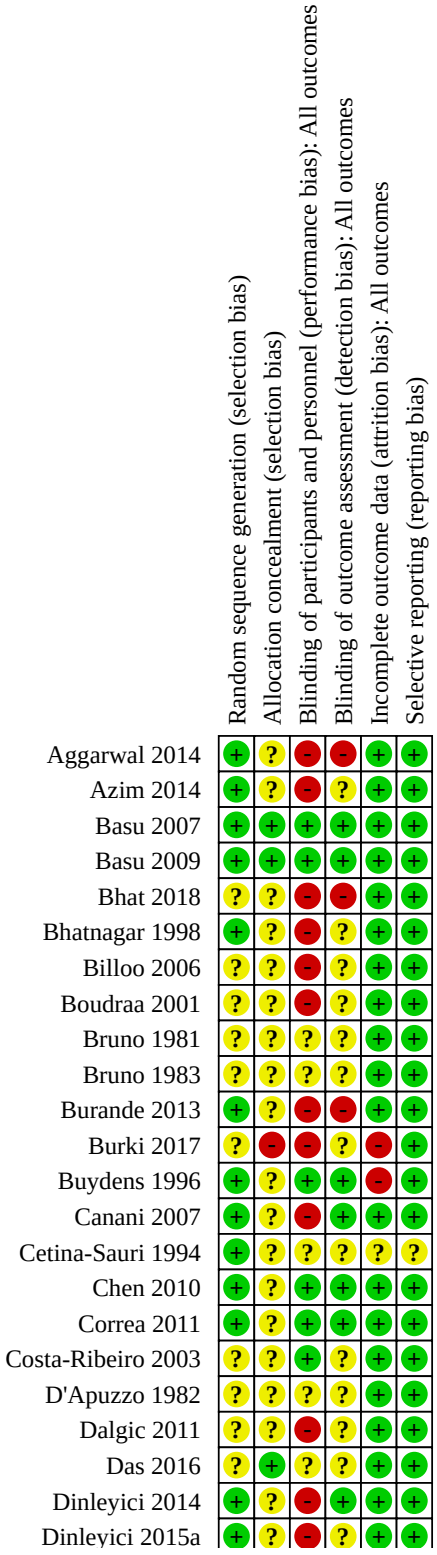


Figure 2. (Continued)

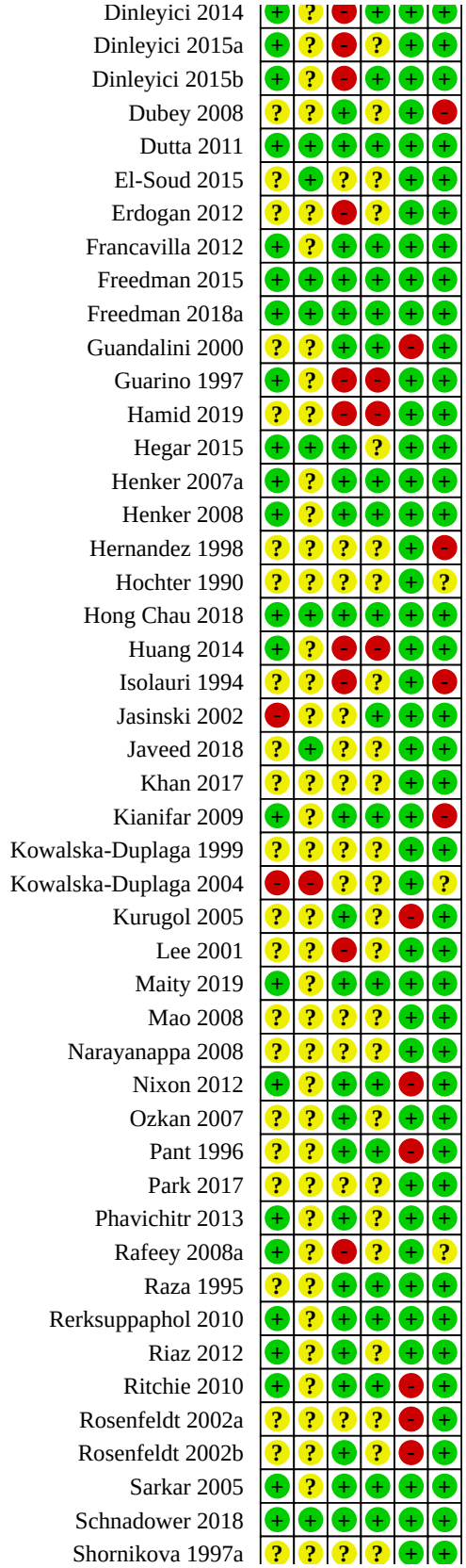


Figure 2. (Continued)

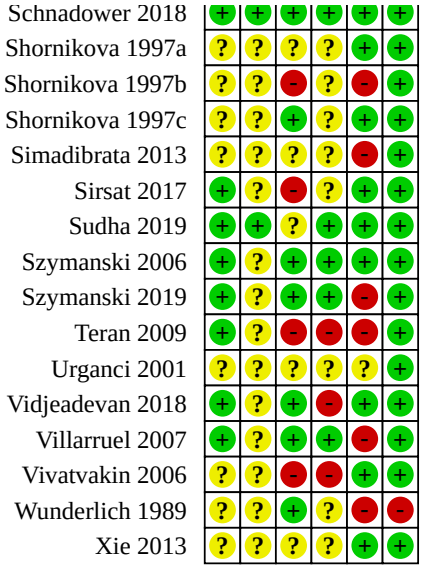
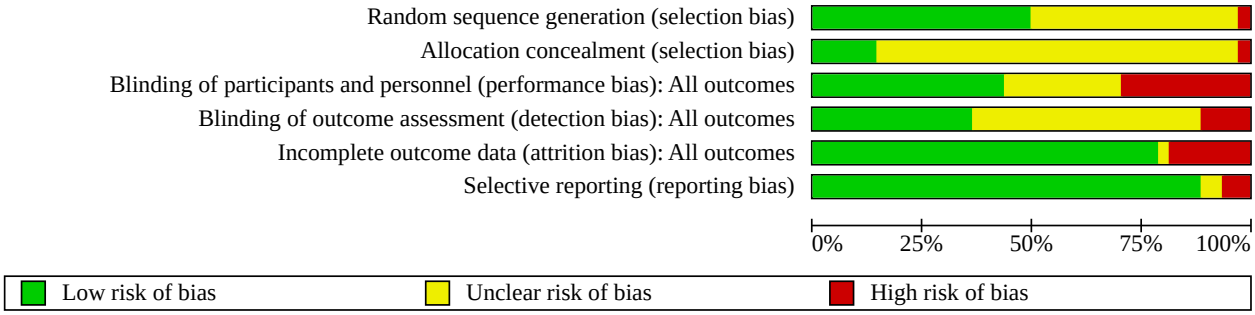


Figure 3. Risk of bias graph: review authors' assessments about each risk of bias item presented as percentages across all included studies.



Effects of interventions

See: **Summary of findings 1** Summary of findings table 1

Primary outcomes

We used random-effects analysis because of marked statistical heterogeneity in findings. The risk of diarrhoea lasting ≥ 48 hours was reduced in people receiving a probiotic compared with controls (36 trials/6053 participants; risk ratio (RR) 0.64, 95% confidence interval (CI) 0.52 to 0.79; Analysis 1.1). Mean duration of diarrhoea was also reduced in the probiotic group (56 trials/9138 participants; mean difference (MD) 21.3 hours, 95% CI 15.7 to 26.9; Analysis 1.2). However, heterogeneity between studies was very high for both primary outcomes and this undermined confidence in estimates of probiotic effect.

A notable finding was that two recently conducted large trials undertaken in children did not show a probiotic effect for the number of children with diarrhoea lasting ≥ 48 hours (Analysis 1.1) or for mean duration of diarrhoea (Analysis 1.2; Freedman 2018a; Schnadower 2018).

The funnel plots are suggestive of publication bias for diarrhoea lasting ≥ 48 hours (Figure 4; Habord test; t = -4.57, P < 0.001) and possibly also mean duration of diarrhoea (Figure 5; Egger's test; t = -3.33, P = 0.002).

Figure 4. Funnel plot of comparison: 1 Primary diarrhoea outcomes, outcome: 1.1 Diarrhoea lasting ≥ 48 hours.

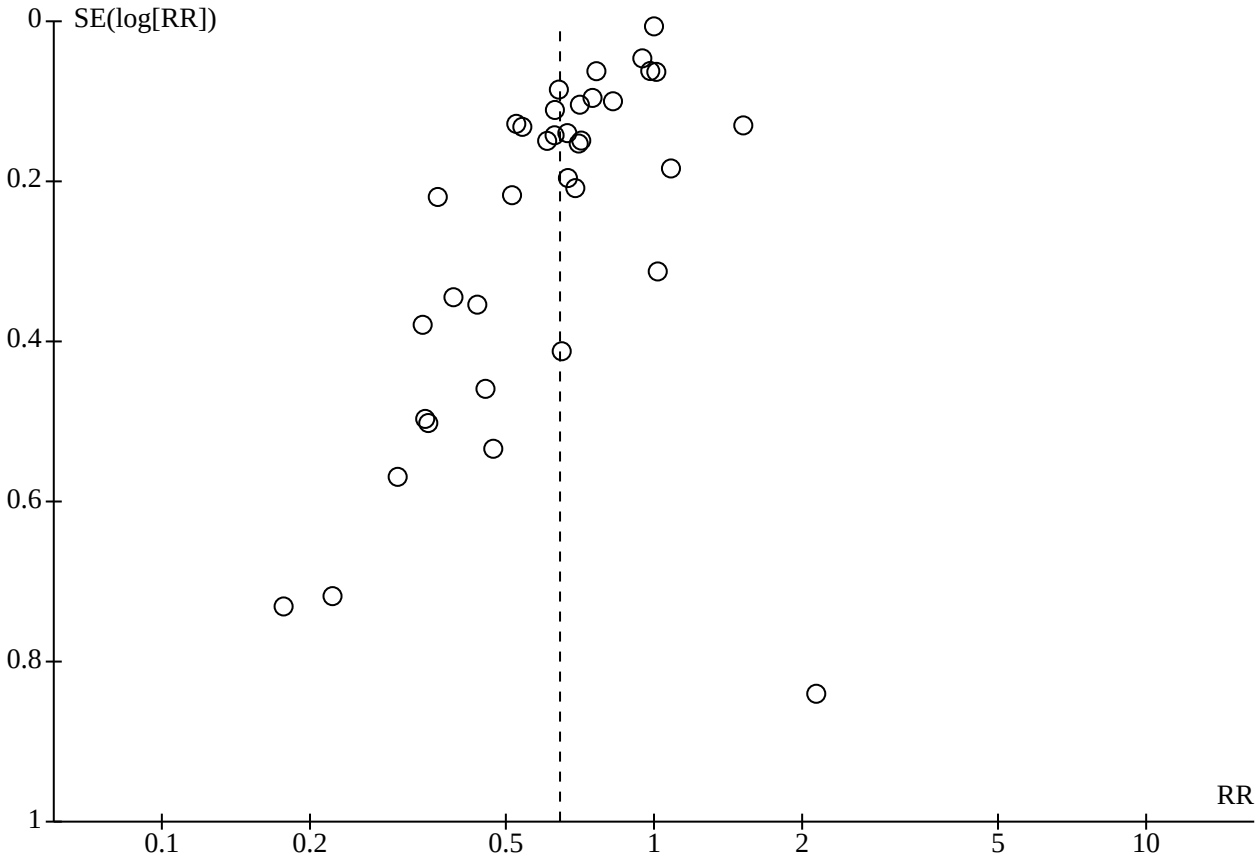
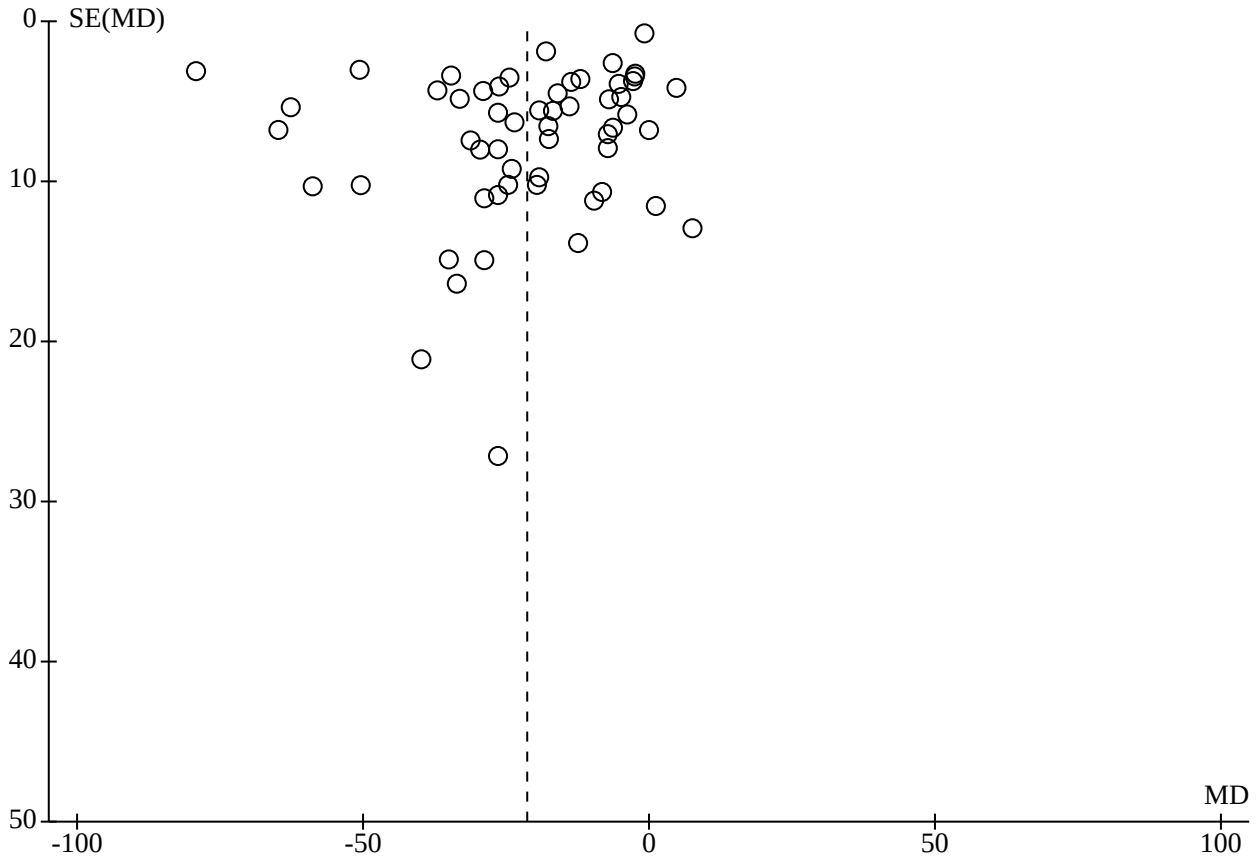


Figure 5. Funnel plot of comparison: 1 Primary diarrhoea outcomes, outcome: 1.2 Mean duration of diarrhoea.



Below we explore the heterogeneity in relation to potential subgroup effects and in relation to risk of bias in the studies, taking into account the likelihood of publication bias.

Secondary outcomes

Secondary outcomes were reported in fewer studies. As for primary outcomes, random-effects analysis was used for all analyses because of marked statistical heterogeneity in findings or high weighting attributed to a small number of studies.

In seven trials (2333 participants) of acute diarrhoea in the community, probiotics did not reduce the risk of hospitalization (RR 1.21, 95% CI 0.86 to 1.69) with consistency in findings between studies (I^2 = 0%; Analysis 2.1). In 24 inpatient trials (4056 participants), duration of hospitalization was reduced in the probiotic arm (MD 18.0 hours, 95% CI 8.8 to 27.3) but with marked statistical heterogeneity (I^2 = 95%; Analysis 2.2). In nine trials (2928 participants), probiotics did not reduce the risk of diarrhoea lasting ≥ 14 days (RR 0.49, 95% CI 0.16 to 1.53) with heterogeneity in findings between studies (I^2 = 60%; Analysis 2.3).

Exploration of heterogeneity

Strain(s) of probiotic organisms

Either or both of the two primary outcomes were reported in five or more studies for three probiotic preparations.

The *Lactobacillus casei* group comprises the closely related species *L casei*, *L paracasei*, and *L rhamnosus,* including *L rhamnosus* GG, and it is difficult to differentiate between these species (Hill 2018). Terminology varied between studies. Amongst studies that specified strain GG, six studies (1557 participants) reported the number of participants with diarrhoea lasting ≥ 48 hours (Analysis 3.1: subgroup 1) and 14 studies (3344 participants) reported mean duration of diarrhoea (Analysis 3.2: subgroup 1). The effects in these analyses were similar to the main analysis of all probiotics, and marked statistical heterogeneity persisted in both analyses.

The effect estimate for diarrhoea lasting ≥ 48 hours among participants taking *S boulardii* was similar to the main analysis but was not statistically significant and findings show marked heterogeneity (RR 0.70, 95% CI 0.37 to 1.33; 9 studies, 1823 participants; I^2 = 99%; Analysis 3.1: subgroup 2). The reduction in duration of diarrhoea was similar to that in the main analysis, and marked statistical heterogeneity persisted (MD 24.6 hours, 95% CI 14.0 to 35.3; 11 studies, 1617 participants; I^2 = 89%; Analysis 3.2: subgroup 2).

In fewer studies, the effect estimate for *L reuteri* in reducing the duration of diarrhoea was similar to that in the main analysis but with less heterogeneity across studies (6 studies/433 participants; MD 22.8 hours, 95% CI 13.7 to 32.0; I^2 = 48%; Analysis 3.2: subgroup 3). However, risk of bias was present in all of the included studies.

Given the high degree of quantitative heterogeneity in studies that evaluated the same probiotic organism, we did not proceed to NMA.

The identity and viability of probiotic organisms were evaluated by bacteriology and molecular methods in seven studies (Freedman 2015; Freedman 2018a; Hong Chau 2018; Mao 2008; Rosenfeldt 2002a; Rosenfeldt 2002b; Schnadower 2018), and were evaluated independently of the study team in two of these studies (Freedman 2015; Schnadower 2018). Hegar 2015 reported that stability of the probiotic organisms at different storage temperatures had been confirmed. Stools were tested for probiotic organisms in eight studies (Chen 2010; Isolauri 1994; Lee 2001; Rosenfeldt 2002a; Rosenfeldt 2002b; Shornikova 1997b; Shornikova 1997c; Szymanski 2006). The identity and viability of the probiotic organisms were not evaluated in 74 studies.

Diarrhoea pathogen

Rotavirus was the only infectious cause of diarrhoea for which sufficient studies reported outcomes to consider meta-analysis. In 20 studies (1414 participants, all of whom were children), the reduction in duration of diarrhoea was similar to that in the main analysis, and marked statistical heterogeneity between studies persisted (MD 22.1 hours, 95% CI 14.2 to 29.9; I^2 = 84%; Analysis 4.1).

Age of participants

For children younger than five years, the effect estimate for diarrhoea lasting ≥ 48 hours was lower than in the main analysis (26 studies, 5033 children; RR 0.72, 95% CI 0.59 to 0.88) and marked statistical heterogeneity persisted (I^2 = 97%; Analysis 5.1: subgroup 1). The reduction in diarrhoea duration was similar to the main analysis, and marked statistical heterogeneity persisted (45 studies, 6697 children; Analysis 5.2).

We were unable to extract data according to the other pre-specified age groups; however, in fewer studies of adults (≥ 18 years; 5 studies, 393 participants), probiotics reduced the RR of diarrhoea lasting ≥ 48 hours to a lesser degree than in the main analysis but with consistency between studies (RR 0.62, 95% CI 0.54 to 0.71; I^2 = 0%; Analysis 5.1: subgroup 2).

Severity of diarrhoea

Diarrhoea lasting ≥ 48 hours was reported in 21 studies (2354 participants) of participants who required admission and therefore were likely to have more severe illness. The effect estimate in these trials (RR 0.62, 95% CI 0.52 to 0.74) was similar to all studies, and marked heterogeneity in findings persisted (I^2 = 75%; Analysis 6.1).

Mean duration of diarrhoea was reported in 36 inpatient studies (5071 participants) and in 8 outpatient studies (828 participants). The effect estimate was similar in these two groups, and marked heterogeneity was present in both analyses (I^2 = 97% and 94%, respectively; Analysis 6.2).

Country mortality stratum

For both diarrhoea lasting ≥ 48 hours and mean duration of diarrhoea, effect estimates were similar when studies were grouped according to mortality stratum (Analysis 7.1; Analysis 7.2).

Geographical region

Effect estimates were also similar when studies were grouped according to geographical region. Statistical heterogeneity persisted in these analyses with the exception of studies done in the Eur-A region (Analysis 8.1: subgroup 3; I^2 = 27%).

Exposure to antibiotics

For both diarrhoea lasting ≥ 48 hours and mean duration of diarrhoea, effect estimates were similar in studies where participants may have been exposed to antibiotics before recruitment and marked statistical heterogeneity between studies persisted (Analysis 9.1; Analysis 9.2).

Treatment of children with zinc

The effect estimate for probiotics on the duration of diarrhoea in children treated with zinc was similar to that in the main analysis, and marked statistical heterogeneity persisted (Analysis 10.1).

Sensitivity analysis for primary outcomes

For both primary outcomes, we conducted sensitivity analysis against each individual risk of bias, examining the effect estimates for low risk against each parameter. This did not explain the heterogeneity (Analysis 11.1; Analysis 11.2).

When analysis was restricted to studies where all indicators of risk of bias were low, there was no heterogeneity with consistent estimates of null effect in the two large studies meeting these criteria for number of participants with diarrhoea lasting ≥ 48 hours between study arms (RR 1.00, 95% CI 0.91 to 1.09; I^2 = 0%; two trials, 1770 participants; Analysis 11.1: subgroup 7). Similarly, for trials reporting mean duration of diarrhoea that were at low risk of bias for all six indices of study quality, no difference was demonstrated between intervention and control (MD 8.6 hours less, 95% CI 29.4 less to 12.1 hours more; 6 trials, 3058 participants). Heterogeneity persisted (I^2 = 97%; Analysis 11.2: subgroup 7).

Given the marked statistical heterogeneity in nearly all analyses that was not explained by sensitivity analysis, we assessed in post hoc analyses whether effect estimates varied according to decade of publication. The effect estimate for diarrhoea lasting ≥ 48 hours was similar according to decade of publication (Analysis 12.1), and the difference between groups was of borderline statistical significance in the most recent studies (from 2010; 15 trials/3972 participants; RR 0.78, 95% CI 0.63 to 0.98; Analysis 12.1; subgroup 4). For mean duration of diarrhoea, effect estimates according to decade of publication were also similar to the main analysis (Analysis 12.2).

Fifteen studies were registered in a trial database. For both primary outcomes, effect estimates were similar to the main analysis in these studies, and marked statistical heterogeneity persisted (Analysis 13.1; Analysis 13.2).

In the light of the marked quantitative and qualitative heterogeneity unexplained by subgroup analysis; the clear evidence of publication bias; and the large, recent, well conducted trials showing null effect, we concluded that the most robust and reliable analysis is for trials with low risk of bias in all parameters, and this analysis we used in our summary of findings table.

Adverse events

Fifty studies reported that no adverse events (AEs) were attributed to the probiotic(s), and two studies stated that no serious AEs (SAEs) were attributed to the probiotic (Phavichitr 2013; Simadibrata

2013). Javeed 2018 reported no deaths in either group. Khan 2017 commented that the probiotic was safe but did not present adverse event data. Henker 2008 reported one participant with a mild hypersensitivity reaction that was possibly related to *E coli* strain Nissle 1917. Schnadower 2018 reported similar rates of adverse events in the two groups, except that wheezing was more common in children receiving *L rhamnosus GG* than in controls (5/472 versus 0/479 children; P = 0.03; borderline statistical significance in view of multiple comparisons); SAEs occurred in a similar number of children in each group. Freedman 2015 reported that AEs including abdominal cramps and rash occurred in both groups but frequency was higher in the control group; no SAEs occurred. Freedman 2018a reported that the frequency of AEs was similar in the two groups; no SAEs occurred in the probiotic group. Szymanski 2019 reported a similar frequency of AEs in both groups; no SAEs occurred. The remaining 17 studies did not report on adverse events.

DISCUSSION

Summary of main results

This review included 82 studies with a total of 12,127 participants. Because of marked heterogeneity in the pooled analyses and high or unclear risk of bias in many studies, we report the main comparisons in studies at low risk of bias in the 'Summary of findings' table. In these studies at low risk of bias, we consider that there was moderate certainty evidence that probiotics probably make little or no difference to the risk of diarrhoea lasting 48 hours or more. We cannot make a reliable estimate of the efficacy of probiotics in reducing the duration of diarrhoea because certainty of evidence was very low.

We do not know whether or not probiotics reduce the duration of hospitalization or diarrhoea lasting 14 or more days due to marked statistical heterogeneity between studies. Probiotics did not prevent hospitalization with acute diarrhoea, with consistency in study findings.

Probiotics were not associated with adverse events, but reporting was limited.

Overall completeness and applicability of evidence

The included trials were undertaken in many different countries from different world regions and, therefore, were adequate to address the main research question. However, most study participants were children, and available data for adults are sparse.

Despite the addition of 36 studies undertaken since our previous review (Allen 2010), there was marked heterogeneity between studies. Effect sizes were similar and heterogeneity persisted in our pre-planned subgroup analyses according to probiotic strain, diarrhoea caused by rotavirus, age, severity of illness, country mortality stratum or region, exposure to antibiotics, treatment with zinc in children, and risk of bias. Between-study heterogeneity may be due to other differences between trials such as the definitions used for "acute diarrhoea" and "the end of the diarrhoeal episode." Also great variability in reported outcomes is evident, which limited data available for meta-analysis for the primary outcomes. Further development of core outcome sets for clinical trials in acute diarrhoea (e.g. to include patient/public perspectives and adult patients), which also include criteria for diagnosis of gastroenteritis (Karas 2016), should help to ensure greater consistency in trial methods and reporting outcomes that will strengthen the evidence base for the treatment of diarrhoea.

The recent 2013 Global Enteric Multicenter Study (GEMS) in children in sub-Saharan Africa and south Asia has highlighted the multiple infectious agents responsible for acute diarrhoea and the importance of bacteria as common diarrhoeal pathogens (Kotloff 2013; Kotloff 2019; Liu 2016b). Although many studies included participants with bacterial diarrhoea or bloody stools, too few studies reported outcomes for these participants for meta-analysis to be performed. Differences in causes of diarrhoea likely account for some of the statistical heterogeneity between studies and have likely changed over time, for example, as a result of immunization programmes such as those for rotavirus. Future studies should determine main infectious causes of diarrhoea and should archive samples for analysis as enteric diagnostic technology evolves.

Confirmation of probiotic identity, viability, and number of organisms by quantitative culture and molecular methods was done in only eight trials but should be standard in research studies (Rijkers 2010; Wolvers 2010).

Although post hoc analysis limited to registered trials did not significantly modify the effect estimate, the absence of published trial protocols for most trials limited our assessment of bias due to selective outcome reporting. In addition, we found that publication bias may have limited the research studies included in this review; a recent systematic review of probiotics in the management of constipation also reported evidence of publication bias (Harris 2019). However, a recent review found no evidence that the source of funding for trials of probiotics in diarrhoea had affected trial results (Saa 2019).

Although most studies reported absence of adverse events due to probiotics, few studies provided a description of the methods used for detecting and classifying adverse events and few reported specific data on adverse events. This is consistent with poor adverse event reporting in probiotic trials in general and highlights the need for improved practice in reporting of harms in probiotic studies especially in vulnerable people (Bafeta 2018; Besselink 2008; Yelin 2019).

Certainty of the evidence

Details of downgrading for GRADE for the few trials at low risk of bias are contained in Summary of findings 1. For diarrhoea lasting 48 hours or longer, certainty of evidence was moderate due to indirectness resulting from the inclusion of only two trials, both of which were conducted in high-income countries, and evaluation of only two probiotics. For mean duration of diarrhoea, certainty of evidence was very low due to marked variability in findings between studies and imprecision in the effect estimate.

Among all trials included in this review, there was evidence of publication bias in trials reporting numbers of participants with diarrhoea lasting 48 hours or longer, with a greater number of smaller studies reporting a positive effect of probiotics (Figure 4). Although less clear, this may have also been the case for studies reporting mean duration of diarrhoea (Figure 5).

There was great variability in the methodological quality of trials, but this did not appear to have contributed to heterogeneity. Heterogeneity was not resolved in sensitivity analysis according to individual parameters of risk of bias nor in subgroup analysis

of trials where risk of bias for all six parameters was low. The importance of careful assessment of risk of bias in studies included in meta-analyses has been highlighted recently (Harris 2019; Schnadower 2019a). Because of the persistence of marked statistical heterogeneity in the subgroup analyses, we also analysed primary outcomes according to decade of publication (Analysis 12.1; Analysis 12.2) and whether or not trials had been registered in a trial database (Analysis 13.1; Analysis 13.2; Kaplan 2015). However, there were no clear differences in effect sizes in these analyses, and heterogeneity persisted.

Based on our criterion of five or more trials reporting the primary outcomes, we pooled data for *Lactobacillus rhamnosus* GG, *Saccharomyces boulardii,* and *Lactobacillus reuteri.* Pooled estimates of probiotic effect for these strains were similar to our overall findings, and statistical heterogeneity persisted for the first two strains. Of note, a recent large, well-conducted trial of *L rhamnosus* GG in children in the USA did not observe a probiotic effect (Schnadower 2018). Trials that evaluated *L reuteri* had less heterogeneity but risk of bias was present in all included studies.

In keeping with clinical management, diarrhoea aetiology was determined in only a minority of studies and meta-analysis was possible only for rotavirus diarrhoea. All of these studies were done in children. For this diarrhoeal pathogen, the effects of probiotics were similar to those in the main analyses, but again with marked statistical heterogeneity and risk of bias in many studies.

Although there was greater consistency among trials of adults (I^2 = 0%), only a few of these trials were included in this analysis and risk of bias was present in many.

We categorized trials according to World Heath Organization (WHO) world region and country mortality stratum (WHO 2001) in an attempt to capture regional differences in diarrhoea aetiology, exposure to infection, and host characteristics. Heterogeneity persisted in these analyses with the exception of studies done in the Eur-A region, where consistency was greater when diarrhoea lasting 48 hours or longer was reported (I^2 = 27%) but marked heterogeneity persisted for the mean duration of diarrhoea (I^2 = 78%), and risk of bias was present in many of the included studies for both outcomes.

Marked statistical heterogeneity and presence of risk of bias were also evident in studies that included people exposed to antibiotics and in the few studies of children treated with zinc.

Agreements and disagreements with other studies or reviews

Our previous review concluded that probiotics appeared to shorten the duration of acute infectious diarrhoea although there was insufficient evidence to recommend a specific probiotic regimen (Allen 2010). In this update, the use of GRADE has highlighted limitations in the evidence and we also found clear evidence of publication bias. As a result, we limited our evaluation to trials at low risk of bias. Analysis of these trials has changed our conclusion as they do not provide evidence of probiotic efficacy.

Other reviews on this topic have also reported marked statistical heterogeneity and low certainty of evidence. A recent systematic review and network meta-analysis of interventions for acute diarrhoea in children reported high statistical heterogeneity for duration of diarrhoea for *L rhamnosus* GG, *S boulardii,* and other probiotics grouped together versus standard treatment and certainty of evidence was graded as low or very low (Florez 2018). A recent update of a meta-analysis of *L rhamnosus* GG in acute diarrhoea in children reported high statistical heterogeneity between studies (Szajewska 2019a). Correspondence following this review highlighted that the effect of the probiotic was not statistically significant when analysis was limited to studies at low risk of bias (Schnadower 2019b), and that marked heterogeneity persisted in these analyses (Szajewska 2019b). Similarly, marked statistical heterogeneity in the duration of diarrhoea was reported in another recent review of *L rhamnosus* GG in paediatric diarrhoea (Li 2019).

A systematic review of *L reuteri* DSM 17938 for treating acute gastroenteritis in children reported marked statistical heterogeneity and very low certainty of evidence for both duration of diarrhoea and duration of hospitalization (Patro-Gołab 2019).

Our findings regarding rotavirus diarrhoea in children are consistent with a review that reported marked heterogeneity between studies (Ahmadi 2015). A recent systematic review that summarised trials of *S boulardii* in children with rotavirus diarrhoea (n = 548 children; five RCTs) reported a modest reduction in diarrhoea duration (MD −0.57 days; 95% CI −0.83 to −0.30) with consistency in findings (I^2 = 0%) and moderate certainty evidence (Padayachee 2019). However, small sample sizes, unclear and inconsistent quality of methodology, and possible reporting bias prevented the authors from making a definitive conclusion regarding the efficacy of *S boulardii* and they emphasised the need for further research.

AUTHORS' CONCLUSIONS

Implications for practice

Our findings do not support the use of probiotics for the treatment of acute infectious diarrhoea. In analysis limited to trials evaluating the same probiotic strain, there was marked heterogeneity in findings and risk of bias in many of the included trials. Our findings do not support recommendations for the use of specific probiotics for acute infectious diarrhoea in children (Floch 2015; Guarino 2018; Sniffen 2018). The challenge of selecting specific probiotics for particular patient groups is highlighted by two well-conducted recent studies that reported negative results (Freedman 2018a; Schnadower 2018).

Implications for research

Given the large number of studies already reported, the ways further research will contribute significantly to the evidence base that informs clinical practice needs careful consideration. The very marked heterogeneity between studies in this and other reviews argues against "core" properties shared by different probiotics that are effective against diarrhoea due to many different infectious agents and its occurrence in different populations and regions (Hill 2014). This finding is consistent with the importance of considering strain-specific effects of probiotics. With the exception of a recent trial in children in the USA that did not find *Lactobacillus rhamnosus GG* to be effective (Schnadower 2018), large-scale, high-quality studies that follow up on previously encouraging findings of specific probiotics in specific populations have not been done. Future studies should focus on probiotics that have evidence of

possessing properties that address specific underlying pathogenic mechanisms, which may be limited to specific infectious agents and populations (Brüssow 2019; Florez 2018; Glanville 2015).

Marked variability in study design likely contributed to the high level of statistical heterogeneity. Future studies should use standardized definitions for acute diarrhoea and resolution of the illness, determine diarrhoea aetiology, and confirm the identity of the probiotic being tested and the number of viable organisms at the point of use.

Finally, we identified evidence of publication bias. Effect estimates may vary according to whether or not trials are registered (Kaplan 2015). To improve the reliability of findings, future systematic reviews of probiotics should consider including only trials that have been registered in a clinical trials database.

ACKNOWLEDGEMENTS

The Academic Editor is Professor Paul Garner and Sign-off Editor is Dr Hellen Gelband.

The editorial base of the Cochrane Infectious Diseases Group (CIDG) is funded by UK aid from the UK government for the benefit of low- and middle-income countries (project number 300342-104). The views expressed do not necessarily reflect the UK government's official policies.

We thank Deirdre Walshe, CIDG Managing Editor, for assistance with undertaking this review; Vittoria Lutje, CIDG Information Specialist for performing the literature searches; and Artemis Koukounari, Statistical Epidemiologist, LSHTM, for advice regarding NMA. We also thank Paul Garner, Marty Chaplin, and Melissa Taylor (CIDG); and external peer reviewers Stephen Freedman, David Schnadower, Phillip I Tarr, Hania Szajewska, and Bartłomiej M Zalewski for their very valuable feedback on a draft of the review.

REFERENCES

References to studies included in this review

Aggarwal 2014 *{published data only}*

Aggarwal S, Upadhyay A, Shah D, Teotia N, Agarwal A, Jaiswal V. Lactobacillus GG for treatment of acute childhood diarrhoea: an open labelled, randomized controlled trial. *Indian Journal Medical Research* 2014;**139**(3):379-85.

Azim 2014 *{published data only}*

Azim K, Sheikh TS, Khan SN. Efficacy of probiotics (Saccharomyces bulardii) in acute watery diarrhoea in children. *Journal of Rawalpindi Medical College (JRMC)* 2014;**18**(2):213-5.

Basu 2007 *{published data only}*

Basu S, Chatterjee M, Ganguly S, Chandra PK. Efficacy of Lactobacillus rhamnosus GG in acute watery diarrhoea of Indian children: a randomised controlled trial. *Journal of Paediatrics and Child Health* 2007;**43**(12):837-42.

Basu 2009 *{published data only}*

Basu S, Paul DK, Ganguly S, Chatterjee M, Chandra PK. Efficacy of high-dose Lactobacillus rhamnosus GG in controlling acute watery diarrhea in Indian children: a randomized controlled trial. *Journal of Clinical Gastroenterology* 2009;**43**(3):208-13.

Bhat 2018 *{published data only}*

Bhat S, Shreekrishna GN, Savio CD. Efficacy of probiotics in acute diarrhoea in children. *International Journal of Contemporary Pediatrics* 2018;**5**(4):1646-50.

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.

Billoo 2006 *{published data only}*

Billoo AG, Memon MA, Khaskheli SA, Murtaza G, Iqbal K, Shekhani MS, et al. Role of a probiotic (Saccharomyces boulardii) in management and prevention of diarrhoea. *World Journal of Gastroenterology* 2006;**12**(28):4557-60.

Boudraa 2001 *{published data only}*

Boudraa G, Benbouabdellah M, Hachelaf W, Boisset M, Desjeux JF, Touhami M. Effect of feeding yogurt versus milk in children with acute diarrhea and carbohydrate malabsorption. *Journal of Pediatric Gastroenterology and Nutrition* 2001;**33**(3):307-13.

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.

Burande 2013 *{published data only}*

Burande MA. Comparison of efficacy of Saccharomyces boulardii strain in the treatment of acute diarrhea in children: a prospective, `single-blind`, randomized controlled clinical trial. *Journal of Pharmacology and Pharmacotherapeutics* 2013;**4**(3):205-8.

Burki 2017 *{published data only}*

Burki MFK, Jabeen F. Efficacy of Saccharomyces boullardii in children with acute diarrhoea. *Medical Forum* 2017;**28**(2):112-6.

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.

Canani 2007 *{published data only}*

Canani RB, Cirillo P, Terrin G, Cesarano L, Spagnuolo MI, Vincenzo A, et al. Probiotics for treatment of acute diarrhea in children: randomised clinical trial of five different preparations. *BMJ* 2007;**335**(7615):340.

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.

Chen 2010 *{published data only}*

Chen CC, Kong MS, Lai MW, Chao HC, Chang KW, Chen SY, et al. Probiotics have clinical, microbiologic, and immunologic efficacy in acute infectious diarrhea. *Pediatric Infectious Diseases Journal* 2010;**29**(2):135-8.

Correa 2011 *{published data only}*

Correa NBO, Penna FJ, Lima FMLS, Nicoli JR, Filho LAP. Treatment of acute diarrhea with Saccharomyces boulardii in Infants. *Journal of Pediatric Gastroenterology and Nutrition* 2011;**53**(5):497–501.

Costa-Ribeiro 2003 *{published data only}*

Costa-Ribeiro H, Ribeiro TC, Mattos AP, Valois SS, Neri DA, Almeida P, et al. Limitations of probiotic therapy in acute, severe dehydrating diarrhea. *Journal of Pediatric Gastroentology and Nutrition* 2003;**36**(1):112-5.

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**(12):1033-5.

Dalgic 2011 *{published data only}*

Dalgic N, Sancar M, Bayraktar B, Pullu M, Hasim O. Probiotic, zinc and lactose-free formula in children with rotavirus diarrhea: are they effective? *Paediatrics International* 2011;**53**:677-82.

Das 2016 *{published data only}*

Das S, Gupta PK, Das RR. Efficacy and safety of Saccharomyces boulardii in acute rotavirus diarrhea: double blind randomized controlled trial from a developing country. *Journal of Tropical Pediatrics* 2016;**62**:464–70.

Dinleyici 2014 *{published data only}*

Dinleyici EC, PROBAGE Study Group, Vandenplas Y. Lactobacillus reuteri DSM 17938 effectively reduces the duration of acute diarrhoea in hospitalised children. *Acta Pædiatrica* 2014;**103**:e300–e305.

Dinleyici 2015a *{published data only}*

Dinleyici EC, Dalgic N, Guven S, Metin O, Yasa O, Kurugol Z, et al. Lactobacillus reuteri DSM 17938 shortens acute infectious diarrhea in a pediatric outpatient setting. *Jornal de Pediatria* 2015;**91**(4):392-6.

Dinleyici 2015b *{published data only}*

Dinleyici EC, Kara A, Dalgic N, Kurugol Z, Arica V, Metin O, et al. Saccharomyces boulardii CNCM I-745 reduces the duration of diarrhoea, length of emergency care and hospital stay in children with acute diarrhoea. *Beneficial Microbes* 2015;**6**(4):415-21.

Dubey 2008 *{published data only}*

Dubey AP, Rajeshwari K, Chakravarty A, Famularo G. Use of VSL#3 in the treatment of rotavirus diarrhea in children: preliminary results. *Journal of Clinincal Gastroenterology* 2008;**42 Suppl 3 Pt 1**:S126-9.

Dutta 2011 *{published data only}*

Dutta P, Mitra U, Dutta S, Rajendran K, Saha TK, Chatterjee MK. Randomised controlled clinical trial of Lactobacillus sporogenes (Bacillus coagulans), used as probiotic in clinical practice, on acute watery diarrhoea in children. *Tropical Medicine and International Health* 2011;**16**(5):555–61.

El-Soud 2015 *{published data only}*

El-Soud NHA, Said RN, Mosallam DS, Barakat NAM, Sabry MA. Bifidobacterium lactis in treatment of children with acute diarrhea. A randomized double blind controlled trial. *Open Access Macedonian Journal of Medical Sciences* 2015;**3**(3):403-7.

Erdogan 2012 *{published data only}*

Erdoğan O, Tanyeri B, Torun E, Gönüllü E, Arslan H, Erenberk U, et al. The comparison of the efficacy of two different probiotics in rotavirus gastroenteritis in children. *Journal of Tropical Medicine* 2012;**787240**:1-5.

Francavilla 2012 *{published data only}*

Francavilla R, Lionetti E, Castellaneta S, Ciruzzi F, Indrio F, Masciale A, et al. Randomised clinical trial: Lactobacillus reuteri DSM 17938 vs. placebo in children with acute diarrhoea - a double-blind study. *Alimentary Pharmacology and Therapeutics* 2012;**36**:363–9.

Freedman 2015 *{published data only}*

Freedman SB, Sherman PM, Willan A, Johnson D, Gouin S, Schuh S. Emergency department treatment of children with diarrhea who attend day care: a randomized multi dose trial of a Lactobacillus helveticus and Lactobacillus rhamnosus combination probiotic. *Clinical Pediatrics* 2015;**54**(12):1158–66.

Freedman 2018a *{published data only}*

Freedman SB, `Williamson-Urquhart` S, Farion KJ, Gouin S, Willan AR, Poonai N, et al. Multicenter trial of a combination probiotic for children with gastroenteritis. *New England Journal of Medicine* 2018;**379**(21):2015-26.

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**(4):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.

Hamid 2019 *{published data only}*

Hamid F, Quaium SM, Rahman A, Hussain T, Islam T. Clinical efficacy of Bacillus clausii probiotic in the management of acute diarrhoea in children. *Chattogram Maa-O-Shishu Hospital Medical College Journal* 2019;**18**(1):14-7.

Hegar 2015 *{published data only}*

Hegar B, Waspada IMI, Gunardi H, Vandenplas Y. A double blind randomized trial showing probiotics to be ineffective in acute diarrhea in Indonesian children. *Indian Journal of Pediatrics* 2015;**82**(5):410–4.

Henker 2007a *{published data only}*

Henker J, Laass M, Blokhin BM, Bolbot YK, Maydannik VG, Elze M, et al. The probiotic *E. coli* strain Nissle 1917 (EcN) stops acute diarrhoea in infants and toddlers. *European Journal of Paediatrics* 2007;**166**(4):311-8.

Henker 2008 *{published data only}*

Henker J, Laass MW, Blokhin BM, Maydannik VG, Bolbot YK, Elze M, et al. Probiotic *E. coli* Nissle 1917 versus placebo for

treating diarrhea of greater than 4 days duration in infants and toddlers. *Pediatric Infectious Disease Journal* 2008;**27**(6):494-9.

Hernandez 1998 *{published data only}*

Hernandez CL, Pineda EE, Jimenez MIR, Lucena MS. Clinical therapeutic effect of *Saccharomyces boulardii* on children with acute diarrhea. *Revista de Enfermedades Infecciosas en Pediatria* 1998;**11**(43):87-9.

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**(12):188-92.

Hong Chau 2018 *{published data only}*

Hong Chau TT, Minh Chau NN, Hoang Le NT, Chuang The H, Voong Vinh P, Nguyen To NT, et al. A double blind, randomized, placebo-controlled trial of Lactobacillus acidophilus for the treatment of acute watery diarrhea in Vietnamese children. *Pediatric Infectious Disease Journal* 2018;**37**(1):35-42.

Huang 2014 *{published data only}*

Huang YF, Liu PY, Chen YY, Nong BR, Huang IF, Hsieh KS, Chen KT. Three-combination probiotic therapy in children with Salmonella and rotavirus gastroenteritis. *Journal of Clinical Gastroenterology* 2014;**48**(1):37-42.

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.

Jasinski 2002 *{published data only}*

Jasinski C, Tanzi MN, Schelotto F, Varela G, Zanetta E, Acuna AM, et al. Efficacy of *Lactobacillus GG* in oral rehydration solution [Efectop del *Lactobacillus casei* administrado en el suero de rehidratacion oral, en el tratamiento de la enfermedad diarreica aguda]. *Pediatrika* 2002;**22**(7):231-43.

Javeed 2018 *{published data only}*

Javeed A, Manzoor S, Wamiq S. Effect of oral Saccharomyces boulardii supplementation on the duration of acute watery diarrhea in children. *Pakistan Journal of Medical and Health Sciences* 2018;**12**(1):212-4.

Khan 2017 *{published data only}*

Khan MA, Khattak MB, Munir A, Naz I. Efficacy of Lactobacillus reuteri in acute watery diarrhea. *Medical Forum* 2017;**28**(11):7-11.

Kianifar 2009 *{published data only}*

Kianifar HR, Farid R, Ahanchian H, Jabbari F, Moghiman T, Sistanian A. Probiotics in the treatment of acute diarrhea in young children. *Iranian Journal of Medical Sciences* 2009;**34**(3):204-7.

Kowalska-Duplaga 1999 *{published data only}*

Kowalska-Duplaga K, Strus M, Heczko P, Krobicka B, Kurowska-Baran D, Mrukowicz JZ. Lactobif, a marketed probiotic product containing *Bifidobacterium ruminantium,* was not effective in the treatment of acute rotavirus diarrhoea in infants. *Gut* 1999;**44**:17-25.

Kowalska-Duplaga 2004 *{published data only}*

Kowalska-Duplaga K, Krzysztof F, Szajewska H, Janiak R. Efficacy of Trilac® in the treatment of acute diarrhoea in infants and young children - a multicentre, randomised, double blind placebo-controlled study. *Pediatria Wspolczesna, Gastroenterologia, Hepatologia i Zywienie Dziecka* 2004;**6**(3):295-9.

Kurugol 2005 *{published data only}*

Kurugol Z, Koturoglu G. Effects of *Saccharomyces boulardii* in children with acute diarrhoea. *Acta Paediatrica* 2005;**94**(1):44-7.

Lee 2001 *{published data only}*

Lee M-C, Lin L-H, Hung K-L, Wu H-Y. Oral bacterial therapy promotes recovery from acute diarrhoea in children. *Acta Paediatrica Taiwan* 2001;**42**(5):301-5.

Maity 2019 *{published data only}*

Maity C, Gupta AK. A prospective, interventional, randomized, double-blind, placebo-controlled clinical study to evaluate the efficacy and safety of Bacillus coagulans LBSC in the treatment of acute diarrhea with abdominal discomfort. *European Journal of Clinical Pharmacology* 2019;**75**(1):21-31.

Mao 2008 *{published data only}*

Mao M, Yu T, Xiong Y, Wang Z, Liu H, Gotteland M, et al. Effect of a lactose-free milk formula supplemented with bifidobacteria and streptococci on the recovery from acute diarrhoea. *Asia Pacific Journal of Clinical Nutrition* 2008;**17**(1):30-4.

Narayanappa 2008 *{published data only}*

Narayanappa D. Randomized double blinded controlled trial to evaluate the efficacy and safety of Bifilac in patients with acute viral diarrhea. *Indian Journal of Pediatrics* 2008;**75**(7):709-13.

Nixon 2012 *{published data only}*

Nixon AF, Cunningham SJ, Cohen HW, Crain EF. The effect of Lactobacillus GG (LGG) on acute diarrheal illness in the pediatric emergency department (PED). *Pediatric Emergency Care* 2012;**28**(10):1048–51.

Ozkan 2007 *{published data only}*

Ozkan TB, Sahin E, Erdemir G, Budak F. Effect of *Saccharomyces boulardii* in children with acute gastroenteritis and its relationship to the immune response. *Journal of International Medical Research* 2007;**35**(2):201-12.

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.

Park 2017 *{published data only}*

Park MS, Kwon B, Ku S, Ji GE. The efficacy of Bifidobacterium longum BORI and Lactobacillus acidophilus AD031 probiotic treatment in infants with rotavirus infection. *Nutrients* 2017;**9**:E887.

Phavichitr 2013 *{published data only}*

Phavichitr N, Puwdee P, Tantibhaedhyangkul R. Cost-benefit analysis of the probiotic treatment of children hospitalized for acute diarrhea in Bangkok, Thailand. *Southeast Asian Journal of Tropical Medicine Public Health* 2013;**44**(6):1065-71.

Rafeey 2008a *{published data only}*

Rafeey M, Ostadrahimi A, Boniadi M, Ghorashi Z, Alizadeh MM, Hadafey V. *Lactobacillus acidophilus* yogurt and supplement in children with acute diarrhea: a clinical trial. *Research Journal of Medical Sciences* 2008;**2**(1):13-8.

Raza 1995 *{published data only}*

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

Rerksuppaphol 2010 *{published data only}*

Rerksuppaphol S, Rerksuppaphol L. Lactobacillus acidophilus and Bifidobacterium bifidum stored at ambient temperature are effective in the treatment of acute diarrhoea. *Annals of Tropical Paediatrics* 2010;**30**:299–304.

Riaz 2012 *{published data only}*

Riaz M, Alam S, Malik A. Efficacy and safety of Saccharomyces boulardii in acute childhood diarrhea: a double blind randomised controlled trial. *Indian Journal of Pediatrics* 2012;**79**(4):478–82.

Ritchie 2010 *{published data only}*

Ritchie BK, Brewster DR, Tran CD, Davidson GP, McNeil Y, Butler RN. Efficacy of *Lactobacillus GG* in Aboriginal children with acute diarrhoeal disease: a randomised clinical trial. *Journal of Pediatric Gastroenterology and Nutrition* 2010;**50**(6):619-24.

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. *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. *Pediatric Infectious Disease Journal* 2002;**21**(5):417-9.

Sarkar 2005 *{published data only}*

Sarker SA, Sultana S, Fuchs GJ, Alam NH, Azim T, Brűssow H, et al. *Lactobacillus paracasei* strain ST11 has no effect on rotavirus but ameliorates the outcome of nonrotavirus diarrhea in children from Bangladesh. *Pediatrics* 2005;**116**(2):e221-8.

Schnadower 2018 *{published data only}*

Schnadower D, Tarr PI, Casper TC, Gorelick MH, Dean M, O'Connell KJ, et al. Lactobacillus rhamnosus GG versus placebo for acute gastroenteritis in children. *New England Journal of Medicine* 2018;**379**(21):2002-14.

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. *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.

Simadibrata 2013 *{published data only}*

Simadibrata M, Ndraha S, Tedjasaputra R, Syam AF, Santi AFA, Rani A. Revealing the effect of probiotic combination Lactobacillus rhamnosus and Lactobacillus acidophilus (Lacidofil®) on acute diarrhea in adult patients. *Journal of Clinical Medicine and Research* 2013;**5**(2):23-8.

Sirsat 2017 *{published data only}*

Sirsat GM, Sankpal DM. Role of Saccharomyces boulardii in management of acute diarrhoea of children - A randomized controlled trial. *MedPulse International Journal of Pediatrics* 2017;**4**(3):68-72.

Sudha 2019 *{published data only}*

Sudha MR, Jayanthi N, Pandey DC, Verma AK. *Bacillus clausii* UBBC-07 reduces severity of diarrhoea in children under 5 years of age: a double blind placebo controlled study. *Benef Microbes* 2019;**10**(2):149-54.

Szymanski 2006 *{published data only}*

Szymanski H, Pejcz J, Jawien M, Chmielarczyk A, Strus M, Heczko PB. Treatment of acute infectious diarrhoea in infants and children with a mixture of three *Lactobacillus rhamnosus* strains -- a randomized, double-blind, placebo-controlled trial. *Alimentary Pharmacology and Therapeutics* 2006;**23**(2):247-53.

Szymanski 2019 *{published data only}*

Szymański H, Szajewska H. Lack of efficacy of Lactobacillus reuteri DSM 17938 for the treatment of acute gastroenteritis: a randomized controlled trial. *Pediatric Infectious Disease Journal* 2019;**38**(10):e237-42.

Teran 2009 *{published data only}*

Teran CG, Teran-Escalera CN, Villarroel P. Nitazoxanide vs. probiotics for the treatment of acute rotavirus diarrhea in children: a randomized, single-blind, controlled trial in Bolivian children. *International Journal of Infectiouos Diseases* 2009;**13**(4):518-23.

Urganci 2001 *{published data only}*

Urganci N, Polat T, Uysalol M, Cetinkaya F. Evaluation of the efficacy of *Saccharomyces boulardii* in children with

acute diarrhoea. *Archives of Gastroenterohepatology* 2001;**20**(3-4):81-3.

Vidjeadevan 2018 *{published data only}*

Vidjeadevan D, Vinoth S, Ramesh S. Role of Saccharomyces boulardii and Bacillus clausii in reducing the duration of diarrhea: a three-armed randomised controlled trial. *International Journal of Contemporary Pediatrics* 2018;**5**(5):1811-4.

Villarruel 2007 *{published data only}*

Villarruel G, Rubio DM, Lopez F, Cintioni J, Gurevech R, Romero G, et al. *Saccharomyces boulardii* in acute childhood diarrhea: a randomised placebo controlled study. *Acta Paediatrica* 2007;**96**(4):538-41.

Vivatvakin 2006 *{published data only}*

Vivatvakin B, Kowitdamrong E. Randomized control trial of live *Lactobacillus acidophilus* plus *Bifidobacterium infantis* in treatment of infantile acute watery diarrhea. *Journal of the Medical Association of Thailand* 2006;**89**:Suppl 3:S126-33.

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. *Journal of International Medical Research* 1989;**17**(4):333-8.

Xie 2013 *{published data only}*

Xie YM, Gao S, Wang LY, Wang ZL. Therapeutic effect of probiotics and oral IgY as supplementary drugs in the treatment of pediatric rotavirus enteritis: a comparative study. *Chinese Journal of Contemporary Pediatrics* 2013;**15**(11):1000-5.

References to studies excluded from this review

Agarwal 2001 *{published data only}*

Agarwal KN, Bhasin SK, Faridi MMA, Mathur M, Gupta S. *Lactobacillus casei* in the control of acute diarrhoea - a pilot study. *Indian Pediatrics* 2001;**38**(8):905-10.

Agarwal 2002 *{published data only}*

Agarwal KN, Bhasin SK. Feasibility studies to control acute diarrhoea in children by feeding fermented milk preparations Actimel and Indian Dahi. *European Journal of Clinical Nutrition* 2002;**56**(Suppl. 4):S56-9.

Ahmadipour 2018 *{published data only (unpublished sought but not used)}*

Ahmadipour S, Motamed F, Mohsenzadeh A, Esfandiarpour B. Probiotic or zinc, which is more effective in treatment of diarrhea in children? *Journal of Pediatric Gastroenterology and Nutrition Conference: 51st Annual Meeting European Society for Paediatric Gastroenterology, Hepatology and Nutrition* 2018;**66**:332.

Alexander 1971 *{published data only}*

Alexander JG. Lactobacillus casei tablets in the treatment of intestinal infection. *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.

Asmat 2018 *{published data only (unpublished sought but not used)}*

Asmat S, Shaukat F, Asmat R, Bakhat H, Asmat TM. Clinical efficacy comparison of Saccharomyces boulardii and lactic acid as probiotics in acute pediatric diarrhea. *Journal of the College of Physicians and Surgeons - Pakistan* 2018;**28**:214-7.

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. *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]. *Médecine et Hygiène* 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**(6):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**(6):396-401.

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**(7):457-63.

Brewster 2004 *{published data only}*

Brewster DR, Ritchie B, McNeil Y, Davidson G, Butler R. Efficacy of probiotic therapy in Aboriginal children with acute diarrheal disease. Journal of Pediatric Gastroenterology and Nutrition 2004;**39**:S404.

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.

Cetina Sauri 1990 *{published data only}*

Cetina-Sauri G, Basto GS. Therapeutic evaluation of children with acute diarrhea. *Tribuna Medica* 1990;**81**(3):141-4.

Chandra 2002 *{published data only}*

Chandra RK. Effect of *Lactobacillus* on the incidence and severity of acute rotavirus diarrhoea in infants. A prospective placebo-controlled double-blind study. *Nutrition Research* 2002;**22**(1):65-9.

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 and Nutrition* 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.

Cui 2004 *{published data only}*

Cui Y-L, Wan F-C, Tang D-L, Wu S-H. Efficacy of *Bacillus coagulans* tablets in the treatment of acute and chronic diarrhoea. *International Journal of Immunotherapy* 2004;**20**(1):17-22.

Czerwionka 2009 *{published data only}*

Czerwionka-Szaflarska M, Murawska S, Swincow G. Evaluation of influence of oral treatment with probiotic and/or oral rehydration solution on course of acute diarrhoea in children. *Przeglad Gastroenterologiczny* 2009;**4**(3):166-72.

Dash 2016 *{published data only}*

Dash DK, Dash M, Mohanty MD, Acharya N. Efficacy of probiotic Saccharomyces boulardii as an adjuvant therapy in acute childhood diarrhoea. *Journal of Nepal Paediatric Society* 2016;**36**(3):250-5.

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.

Eren 2010 *{published data only}*

Eren M, Dinleyici EC, Vandenplas Y. Clinical efficacy comparison of *Saccharomyces boulardii* and yogurt fluid in acute non-bloody diarrhea in children: a randomized, controlled, open label study. *American Journal of Tropical Hygiene* 2010;**82**(3):488-91.

Escribano 2018 *{published data only (unpublished sought but not used)}*

Escribano J, Ferre N, Gispert-Llaurado M, Luque V, Rubio-Torrents C, Zaragoza-Jordana M, et al. Bifidobacterium longum subsp infantis CECT7210-supplemented formula reduces diarrhea in healthy infants: a randomized controlled trial. *Pediatric Research* 2018;**83**:1120-8.

Fang 2009 *{published data only}*

Fang SB, Lee H-C, Hu J-J, Hou S-Y, Liu H-L, Fang H-W. Dose-dependent effect of *Lactobacillus rhamnosus* on quantitative reduction of faecal rotavirus shedding in children. *Journal of Tropical Pediatrics* 2009;**55**(5):297-301.

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.

Freedman 2018b *{published data only}*

Freedman S, Williamson-Urquharta S, Farionb K, Gouinc S, Willand A, Poonaie N, et al. "Probiotics in acute gastroenteritis-benefit or harm?: a multicenter, randomized, double-blind, placebo-controlled clinical trial" in North American Congress of Clinical Toxicology (NACCT) Abstracts 2018. *Clinical Toxicology* 2018;**56**(10):912-1092.

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**(1):75-7.

Grandi 2009 *{published data only}*

Grandi G, Medina M, Soria R, Teran C, Araya M. Probiotics in the management of acute rotavirus diarrhea in Bolivian children: a randomized, double-blind, controlled trial of two different preparations. In: Pediatric Research. Vol. 67. 2010:447 (abstract 10).

Grandy 2010 *{published data only}*

Grandy G, Medina M, Soria R, Terán CG, Araya M. Probiotics in the treatment of acute rotavirus diarrhoea. A randomized, double-blind, controlled trial using two different probiotic preparations in Bolivian children. *BMC Infectious Diseases* 2010;**10**:253.

Hafeez 2002 *{published data only}*

Hafeez A, Tariq P, Ali S, Kundi ZU, Khan A, Hassan M. The efficacy of *Saccharomyces boulardii* in the treatment of acute watery diarrhoea in children: a multicentre randomized controlled trial. *Journal of College of Physicians and Surgeons Pakistan* 2002;**12**(7):432-4.

Henker 2007b *{published data only}*

Henker J, Blokhin BM, Bolbot YK, Maydannik VG. Acute diarrhoea in infants and small children. Successful adjuvant therapy with the probiotic Mutaflor [Akute diarrhő bei säuglingen und kleinkindern. Erfolgreiche adjuvante therapie mit dem probiotikum Mutaflor]. *Pädiat. Prax* 2007;**71**:605-10.

Heydarian 2010 *{published data only}*

Heydarian F, Kianifar HR, Ahanchian H, Khakshure A, Seyedi J, Moshirian D. A comparison between traditional yogurt and probiotic yogurt in non-inflammatory acute gastroenteritis. *Saudi Medical Journal* 2010;**31**(3):280-3.

Htwe 2008 *{published data only}*

Htwe K, Yee KS, Tin M, Vandenplas Y. Effect of *Saccharomyces boulardii* in the treatment of acute watery diarrhea in Myanmar children: a randomized control study. *American Journal of Tropical Medicine and Hygiene* 2008;**78**(2):214-6.

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.

Jimenez-Rodriguez 2018 *{published data only}*

Jimenez-Rodriguez C, Jimenez-Diaz J, Hernandez-Martinez F, Rodriguez-De-vera B. Efficacy of probiotics against acute diarrhoea in warm areas. In: Annals of Nutrition and Metabolism Conference: 9th workshop probiotics and prebiotics. Vol. 72. 2018.

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.

Khan 2012 *{published data only}*

Khan A, Javed T, Chishti AL. Clinical efficacy of use of probiotic "Saccharomyces boulardii" in children with acute watery diarrhea. *Pakistan Pediatric Journal* 2012;**36**(3):122-7.

Khanna 2005 *{published data only}*

Khanna V, Seema A, Ashraf M, Abida M. Efficacy of tyndalized *Lactobacillus acidophilus* in acute diarrhoea. *Indian Journal of Pediatrics* 2005;**72**(11):935-8.

Khoshdel 2018 *{published data only}*

Khoshdel A, Kasiri KA, Salehi S, Sedehi M. Effect of probiotics in the treatment of acute noninflammatory diarrhea in hospitalized children aged 2–10 years. *International Journal of Pharmaceutical Investigation* 2018;**8**:200-4.

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.

Lahiri 2015a *{published data only}*

Lahiri K, D'Souza J, Gahlowt P. Beneficial role of probiotic in acute childhood diarrhoea. *Journal of Harmonized Research in Medical and Health Science* 2015;**2**(2):26-30.

Lahiri 2015b *{published data only}*

Lahiri K, Jadhav K, Gahlowt P, Najmuddin F. Bacillus clausii as an adjuvant therapy In acute childhood diarrhoea. *IOSR Journal of Dental and Medical Sciences* 2015;**14**(5):74-6.

Lei 2006 *{published data only}*

Lei V, Friis H, Michaelsen KF. Spontaneously fermented millet product as a natural probiotic treatment for diarrhea in young children: an intervention study Northern Ghana. *International Journal of Food Microbiology* 2006;**110**(3):246-53.

Le Leyur 2010 *{published data only}*

Le Luyer B, Makhoul G, Duhamel JF. A multicentric study of a lactose free formula supplemented with *Saccharomyces boulardii* in children with acute diarrhea. *Archives de Pédiatrie* 2010;**17**(5):459-65.

Lievin Le-Maol 2007 *{published data only}*

Lievin-Le Maol V, Sarrazin-Davilla LE, Servin AL. An experimental study and a randomized, double-blind, placebo-controlled clinical trial to evaluate the antisecretory activity of *Lactobacillus acidophilus* strain LB against non-rotavirus diarrhea. *Pediatrics* 2007;**120**(4):795-803.

Lin 2009 *{published data only}*

Lin JS, Chiu YH, Lin NT, Chu CH, Huang KC, Liao KW, et al. Different effects of probiotic species/strains on infections in

preschool children: a double-blind, randomized, controlled study. *Vaccine* 2009;**27**(7):1073-9.

Magreiter 2006 *{published data only}*

Margreiter M, Ludl K, Phleps W, Kaehler ST. Therapeutic value of a *Lactobacillus gasseri* and *Bifdobacterium longum* fixed bacterium combination in acute diarrhea: a randomized, double-blind, controlled clinical trial. *International Journal of Clinical Pharmacology and Therapeutics* 2006;**44**(5):207-15.

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.

Maragkoudaki 2018 *{published data only (unpublished sought but not used)}*

Maragkoudaki M, Chouliaras G, Moutafi A, Thomas A, Orfanakou A, Papadopoulou A. Efficacy of an oral rehydration solution enriched with Lactobacillus reuteri DSM 17938 and zinc in the management of acute diarrhoea in infants: a randomized, double-blind, placebo-controlled trial. *Nutrients* 2018;**10**(9):pii: E1189.

Maugo 2012 *{published data only}*

Maugo BM. Effectiveness of *Bacillus clausii* in reducing duration of illness in acute diarrhoea in children 6–59 months of age admitted with severe dehydration. University of Nairobi, Kenya 2012.

Mazo 2006 *{published data only}*

Mazo SA, Arias SA. Efficacy and safety of milk fermented by lactobacillus (kumis) in nutritional recovery of undernourished children and control of their diarrhoea episodes. *Revista Facultad Nacional de Salud Pública* 2006;**24**(2):83-97.

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.

Misra 2009 *{published data only}*

Misra S, Sabui TK, Pal NK. A randomized controlled trial to evaluate the efficacy of *Lactobacillus GG* in infantile diarrhea. *Journal of Pediatrics* 2009;**155**(1):129-32.

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.

Moraes 2001 *{published data only}*

Moraes E, Chinzon D, Coelho LG, Fernandes TF, Haddad MT, et al. A multicentric, randomised, investigator-blind, parallel group study to assess the efficacy, safety and tolerability of *Racecadotril* versus *Saccharomyces boulardii* in the treatment of acute diarrhoea in adults [Estudo multicêntrico de grupos paralelos, randomizado, cego para o investigador, para avaliar a eficácia, segurança e tolerabilidade do racecadotril versus Saccharomyces boulardii no tratamento da diarréia aguda em adultos]. *Revista Brasileira de Medicina* 2001;**58**(1-2):65-74.

Niv 1963 *{published data only}*

Niv M, Levy W, Greenstein NM. Yogurt in the treatment of infantile diarrhea. *Clinical Pediatrics* 1963;**2**(7):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.

Pashapour 2006 *{published and unpublished data}*

Pashapour N, Iou SG. Evaluation of yogurt effect on acute diarrhea in 6-24-month-old hospitalized infants. *Turkish Journal of Pediatrics* 2006;**48**(2):115-8.

Pearce 1974 *{published data only}*

Pearce JL, Hamilton JR. Controlled trial of orally administered lactobacilli in acute infantile diarrhea. *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.

Perez 2019 *{published data only}*

Perez M, De Castro J-A, Guno MJ. Coddle study: Bacillus clausii as an adjunctive treatment of acute community-acquired diarrhoea in Filipino children. *Journal of Pediatric Gastroenterology and Nutrition* 2019;**68**(S1):477.

Pernica 2017 *{published data only}*

Pernica JM, Steenhoff AP, Mokomane M, Moorad B, Lechiile K, Smieja M, et al. Rapid enteric testing to permit targeted antimicrobial therapy, with and without Lactobacillus reuteri probiotics, for paediatric acute diarrhoeal disease in Botswana: a pilot, randomized, factorial, controlled trial. *PLoS ONE* 2017;**12**(10):e0185177.

Rafeey 2008b *{published data only}*

Rafeey M, Ghojazadeh M, Hadari V. Probiotics in children with acute diarrhea. In: WCPGHAN 3: World Congress of Pediatric Gastroenterology, Hepatology and Nutrition. 2008:129-35.

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 Médecine Interne* 1991;**142**(1):64-5.

Salazar-Lindo 2004 *{published data only}*

Salazar-Lindo E, Miranda-Langschwager P, Campos-Sanchez M, Chea-Woo E, Bradley Sack R. *Lactobacillus casei* strain GG in the treatment of infants with acute watery diarrhoea: a randomised, double-blind, placebo controlled clinical trial. BMC Pediatrics 2004;**4**(18). [http://www.biomedcentral.com/1471-2431/4/18]

Salazar-Lindo 2007 *{published data only}*

Salazar-Lindo E, Figueroa-Quintanilla D, Caciano MI, Reto-Valiente V, Chauviere G, Colin P, et al. Effectiveness and safety of *Lactobacillus LB* in the treatment of mild acute diarrhea in children. *Journal of Paediatric Gastroenterology and Nutrition* 2006;**44**(5):571-6.

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.

Savas-Erdeve 2009 *{published data only}*

Savas-Erdeve S, Gökay S, Dallar Y. Efficacy and safety of *Saccharomyces boulardii* in amebiasis-associated diarrhea in children. *Turkish Journal of Pediatrics* 2009;**51**(3):220-4.

Schrezenmeir 2004 *{published data only}*

Schrezenmeir J, Heller K, McCue M, Llamas C, Lam W, Burrow H, et al. Benefits of oral supplementation with and without synbiotics in young children. *Clinical Paediatrics* 2004;**43**:239-49.

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**(1):74-80.

Sharif 2017 *{published data only}*

Sharif A, Kashani HH, Nasri E, Soleimani Z, Sharif MR. The role of probiotics in the treatment of dysentery: a randomized double-blind clinical trial. *Probiotics and Antomicrobial Proteins* 2017;**9**(4):380-5.

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.

Sindhu 2014 *{published data only}*

Sindhu KNC, Sowmyanarayanan TV, Paul A, Babji S, Ajjampur SSR, Priyadarshini S, et al. Immune response and intestinal permeability in children with acute gastroenteritis treated with Lactobacillus rhamnosus GG: a randomized, double-blind, placebo-controlled trial. *Clinical Infectious Diseases* 2014;**58**(8):1107–15.

Singh 1987 *{published data only}*

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

Singh 2018 *{published data only}*

Singh M, Alam MS, Iqbal SMJ. Comparison of clinical efficacy of Saccharomyces boulardii with yogurt in acute watery diarrhea in children. *Pakistan Paediatric Journal* 2018;**42**(3):167-71.

Sudarmo 2003 *{published data only}*

Sudarmo SM, Ranuh RG, Rochim A, Soeparto P. Management of infant diarrhea with high-lactose probiotic-containing formula. *Southeast Asian Journal of Tropical Medicine and Public Health* 2003;**34**(4):845-8.

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.

Szymanski 2005 *{published data only}*

Szymanski H, Pejcz J, Jawien M, Kucharska A, Strus M, Heczko PB. Treatment of acute infectious diarrhoea in children with a mixture of three new *Lactobacillus rhamnosus* strains (573L/1,573L/2, 573L/3). A randomized, double-blind, placebo-controlled trial. *Journal of Pediatric Gastroenterology and Nutrition* 2005;**40**(5):652.

Táborská 1997 *{published data only}*

Táborská J, Pazdiora P. Smecta and *Lactobacillus acidophilus* ND in the treatment of acute diarrhoea in children [Smecta a *Lactobacillus acidophilus* ND v lécbe akutních detských prujmu]. *Ceskoslovenská Pediatrie* 1997;**52**(1):29-33.

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 Campylobacter enteritis. *Acta Paediatrica Japonica* 1987;**29**(1):160-7.

Urtula 2009 *{published data only}*

Urtula RP, Dacula CE. Bacillus clausii and adjunct treatment for pediatric patients with acute non-bloody diarrhea: a randomized, controlled clinical trial. *International Journal of Probiotics and Prebiotics* 2009;**4**(2):102-3.

Zareen 2018 *{published data only}*

Zareen A, Haq R, Salem M, Iqbal MM. Effects of probiotics in shortening the duration of acute diarrhea; a randomized control study. *Pakistan Journal of Medical and Health Sciences* 2018;**12**:471-3.

References to ongoing studies

CTRI/2017/08/009543 *{published data only}*

CTRI/2017/08/009543. Effect of probiotic Bacillus clausii UBBC07 in children with Acute Diarrhoea. http://ctri.nic.in/Clinicaltrials/advsearch.php 29 August 2017.

CTRI/2018/04/013360 *{published data only}*

CTRI/2018/04/013360. Efficacy of Lactobacillus sporogenes in treating acute diarrhoea in adults-randomised control study. http://ctri.nic.in/Clinicaltrials/advsearch.php 19 April 2018.

CTRI/2018/06/014480 *{published data only}*

CTRI/2018/06/014480. A multicentric, randomized, double blind, placebo controlled trial to assess the efficacy and safety of Saccharomyces boulardii CNCM-I 3799 Bacillus subtilis CU – 1 combination for treatment of acute diarrhoea in Indian children. http://ctri.nic.in/Clinicaltrials/advsearch.php 6 August 2018.

IRCT2017010312437N2 *{published data only}*

IRCT2017010312437N2. Evaluation of the effect of ORS with probiotics, zinc and vitamin A on diarrhea in children, a double blind clinical trial. https://en.irct.ir/trial/12487 17 August 2017.

IRCT2017090812897N3 *{published data only}*

IRCT2017090812897N3. The effect of yeast probiotic (Saccharomyces boulardii) on acute diarrhea in children. https://en.irct.ir/trial/12898 7 October 2017.

ISRCTN18444252 *{published data only}***ISRCTN**

ISRCTN18444252. Probiotics for treatment of acute childhood diarrhea. https://doi.org/10.1186/ISRCTN18444252 23 February 2018.

NCT03539913 *{published data only}*

NCT03539913. Efficacy and Safety of Probiotics in the Treatment of Acute Gastroenteritis in Children (SABINA). https://clinicaltrials.gov/ct2/show/NCT03539913 30 May 2018.

NCT03684538 *{published data only}*

NCT03684538. Efficacy of probiotics vs. zinc vs. probiotics-zinc combination on acute diarrhea in children. https://clinicaltrials.gov/ct2/show/NCT03684538 25 September 2018.

Additional references

Ahmadi 2015

Ahmadi E, Alizadeh-Navaei R, Sadegh Rezai M. Efficacy of probiotic use in acute rotavirus diarrhea in children: a systematic review and meta-analysis. *Caspian Journal of Internal Medicine* 2015;**6**(4):187-95.

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.

Applegate 2013

Applegate JA, Fischer Walker CL, Ambikapathi R, Black RE. Systematic review of probiotics for the treatment of community-acquired acute diarrhea in children. *BMC Public Health* 2013;**13**(Supplement 3):s16.

Bafeta 2018

Bafeta A, Koh M, Riveros C, Ravaud P. Harms reporting in randomized controlled trials of interventions aimed at modifying microbiota: a systematic review. *Annals of Internal Medicine* 2018;**169**(4):240-7. [DOI: 10.7326/m18-0343]

Besselink 2008

Besselink MG, van Santvoort HC, Buskens E, Boermeester MA, van Goor H, Timmerman HM, et al. Probiotic prophylaxis in predicted severe acute pancreatitis: a randomised, double-blind, placebo-controlled trial. *Lancet* 2008;**371**(9613):651-9. [DOI: 10.1016/S0140-6736(08)60207-X]

Black 1986

Black RE. Pathogens that cause traveler's diarrhea in Latin America and Africa. *Reviews of Infectious Diseases* 1986;**8**(Suppl 2):S131-5.

Brüssow 2019

Brüssow H. Probiotics and prebiotics in clinical tests: an update. *F1000Research* 2019;**8**(F1000 Faculty Rev):1157.

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.

Das 2014

Das JK, Salam RA, Bhutta ZA. Global burden of childhood diarrhoea and interventions. *Current Opinion in Infectious Diseases* 2014;**27**(5):451-8.

Doron 2015

Doron S, Snydman DR. Risk and safety of probiotics. *Clinical Infectious Diseases* 2015;**60**(Supplement 2):s129-34.

Fedorowicz 2011

Fedorowicz Z, Jagannath VA, Carter B. Antiemetics for reducing vomiting related to acute gastroenteritis in children and adolescents. *Cochrane Database of Systematic Reviews* 2011, Issue 9. Art. No: CD005506. [DOI: 10.1002/14651858.CD005506.pub5]

Fischer-Walker 2012

Fischer Walker CL, Perin J, Aryee MJ, Boschi-Pinto C, Black RE. Diarrhoea incidence in low and middle income countries in 1990 and 2010: a systematic review. *BMC Public Health* 2012;**12**:220.

Floch 2015

Floch MH, Walker WA, Sanders ME, Nieuwdorp M, Kim AS, Brenner DA, et al. Recommendations for probiotic use - 2015 update: proceedings and consensus opinion. *Journal of Clinical Gastroenterology* 2015;**49 Suppl 1**:S69-73.

Florez 2018

Florez ID, Veroniki A-A, Al Khalifah R, Yepes-Nuñez JJ, Sierra JM, Vernooij RWM, et al. Comparative effectiveness and safety of interventions for acute diarrhea and gastroenteritis in children: a systematic review and network meta-analysis. *PLoS ONE* 2018;**13**:e0207701.

Fontaine 1998

Fontaine O, Gore SM, Pierce NF. Rice-based oral rehydration solution for treating diarrhoea. *Cochrane Database of Systematic Reviews* 1998, Issue 4. Art. No: CD001264. [DOI: 10.1002/14651858.CD001264.pub2]

Gadewar 2005

Gadewar S, Fasano A. Current concepts in the evaluation, diagnosis and management of acute infectious diarrhea. *Current Opinion in Pharmacology* 2005;**5**(6):559-65.

Glanville 2015

Glanville J, King S, Guarner F, Hill C, Sanders ME. A review of the systematic review process and its applicability for use in evaluating evidence for health claims on probiotic foods in the European Union. *Nutrition Journal* 2015;**14**:16.

Gregorio 2016

Gregorio GV, Gonzales MLM, Dans LF, Martinez EG. Polymer-based oral rehydration solution for treating acute watery diarrhoea. *Cochrane Database of Systematic Reviews* 2016, Issue 12. Art. No: CD006519. [DOI: 10.1002/14651858.CD006519.pub3]

Guarino 2014

Guarino A, Ashkenazi S, Gendrel D, Lo Vecchio A, Shamir R, Szajewska H. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition/European Society for Pediatric Infectious Diseases evidence-based guidelines for the management of acute gastroenteritis in children in Europe: update 2014. *Journal of Pediatric Gastroenterology and Nutrition* 2014;**59**(1):132-52.

Guarino 2015

Guarino A, Guandalini S, Lo Vecchio A. Probiotics for prevention and treatment of diarrhea. *Journal of Clinical Gastroenterology* 2015;**49**(Supplement 1):s37-45.

Guarino 2018

Guarino A, Lo Vecchio A, Dias JA, Berkley JA, Boey C, Bruzzese D, et al. Universal recommendations for the management of acute diarrhea in nonmalnourished children. *Journal of Pediatric Gastroenterol Nutr* 2018;**67**:586-93.

Guarner 2012

Guarner F, Khan AG, Garisch J, Eliakim R, Gangl A, Thompson A, et al. World Gastroenterology Organisation global guidelines: probiotics and prebiotics. *Journal of Clinical Gastroenterology* 2012;**46**(6):468-81.

Guyatt 2011

Guyatt GH, Oxman AD, Schünemann HJ, TugwellP, Knottnerus A. GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. *Journal of Clinical Epidemiology* 2011;**64**:380–2.

Halloran 2019

Halloran K, Underwood MA. Probiotic mechanisms of action. *Early Human Development* 2019;**135**:58-65.

Harris 2019

Harris RG, Neale EP, Ferreira I. When poorly conducted systematic reviews and meta-analyses can mislead: a critical appraisal and update of systematic reviews and meta-analyses examining the effects of probiotics in the treatment of functional constipation in children. *American Journal of Clinical Nutrition* 2019;**110**(1):177–95.

Hartling 2006

Hartling L, Bellemare S, Wiebe N, Russell KF, Klassen TP, Craig WR. Oral versus intravenous rehydration for treating dehydration due to gastroenteritis in children. *Cochrane Database of Systematic Reviews* 2006, Issue 3. Art. No: CD004390. [DOI: 10.1002/14651858.CD004390.pub2]

Hempel 2011

Hempel S, Newberry S, Ruelaz A, Wang Z, Miles JNV, Suttorp MJ, et al. Safety of probiotics used to reduce risk and prevent or treat disease. *Evidence Reports/Technology Assessments* 2011;**200**:1-645.

Higgins 2012

Higgins JPT, Jackson D, Barrett JK, Lu G, Ades AE, White IR. Consistency and inconsistency in network metaanalysis: concepts and models for multi-arm studies. *Research Synthesis Methods* 2012;**3**(2):98-110.

Hill 2014

Hill C, Guarner F, Reid G, Gibson GR, Merenstein DJ, Pot B, et al. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. *Nature Reviews Gastroenterology and Hepatology* 2014;**11**(8):506-14.

Hill 2018

Hill D, Sugrue I, Tobin C, Hill C, Stanton C, Ross RP. The Lactobacillus casei group: history and health related applications. *Frontiers in Microbiology* 2018;**9**:2107. [DOI: 10.3389/fmicb.2018.02107]

Kaplan 2015

Kaplan RM, Irvin VL. Likelihood of null effects of large NHLBI clinical trials has increased over time. *PLoS ONE* 2015;**10**(8):e0132382.

Karas 2016

Karas J, Ashkenazi S, Guarino A, Lo Vecchio A, Shamir R, Vandenplas Y, et al. Developing a core outcome measurement set for clinical trials in acute diarrhoea. *Acta Paediatrica* 2016;**105**(4):e176-80.

Kotloff 2013

Kotloff KL, Nataro JP, Blackwelder WC, Nasrin D, Farag TH, Panchalingam S, et al. Burden and aetiology of diarrhoeal disease in infants and young children in developing countries (the Global Enteric Multicenter Study, GEMS): a prospective, case-control study. *Lancet* 2013;**382**(9888):209-22.

Kotloff 2019

Kotloff KL, Nasrin D, Blackwelder WC, Wu Y, Farag T, Panchalingham S, et al. The incidence, etiology and adverse clinical consequences of less severe diarrheal episodes among infants and children residing in developing countries: a 12-month follow-on investigation to the Global Enteric Multicenter Study (GEMS). *Lancet Global Health* 2019;**7**:e570-86.

Lazzerini 2016

Lazzerini M, Wanzira H. Oral zinc for treating diarrhoea in children. *Cochrane Database of Systematic Reviews* 2016, Issue 12. Art. No: CD005436. [DOI: 10.1002/14651858.CD005436.pub4]

Li 2019

Li YT, Xu H, Ye JZ, Wu WR, Shi D, Fang DQ, et al. Efficacy of Lactobacillus rhamnosus GG in treatment of acute pediatric diarrhea: a systematic review with meta-analysis. *World Journal of Gastroenterology* 2019;**25**(33):4999-5016.

Liu 2016a

Liu L, Oza S, Hogan D, Chu Y, Perin J, Zhu J, et al. Global, regional, and national causes of child mortality in 2000-13, with projections to inform post-2015 priorities: an updated systematic analysis. *Lancet* 2016;**388**:3027-35.

Liu 2016b

Liu J, Platts-Mills JA, Juma J, Kabir F, Nkeze J, Okoi C, et al. Use of quantitative molecular diagnostic methods to identify causes of diarrhoea in children: a reanalysis of the GEMS case-control study. *Lancet* 2016;**388**(10051):1291-301.

Padayachee 2019

Padayachee M, Visser J, Viljoen E, Musekiwa A, Blaauw R. Efficacy and safety of Saccharomyces boulardii in the treatment of acute gastroenteritis in the paediatric population: a systematic review. *South African Journal of Clinical Nutrition* 2019;**32**:58-69.

Patro-Gołab 2019

Patro-Gołab B, Szajewska H. Systematic review with meta-analysis: Lactobacillus reuteri DSM 17938 for treating acute gastroenteritis in children. An update. *Nutrients* 2019;**11**(11):2762.

Pérez-Gaxiola 2018

Pérez-Gaxiola G, Cuello-García CA, Florez ID, Pérez-Pico VM. Smectite for acute infectious diarrhoea in children. *Cochrane Database of Systematic Reviews* 2018, Issue 4. Art. No: CD011526. [DOI: 10.1002/14651858.CD011526.pub2]

Rijkers 2010

Rijkers GT, Bengmark S, Enck P, Haller D, Herz U, Kaolliomaki M, et al. Guidance for substantiating the evidence for beneficial effects of probiotics: current status and recommendations for future research. *Journal of Nutrition* 2010;**140**(3):671S-6S.

Saa 2019

Saa C, Bunout D, Hirsch S. Industry funding effect on positive results of probiotic use in the management of acute diarrhea: a systematized review. *European Journal of Gastroenterology & Hepatology* 2019;**31**:289–302.

Salari 2012

Salari P, Nikfar S, Abdollahi M. A meta-analysis and systematic review on the effect of probiotics in acute diarrhea. *Inflammation and Allergy Drug Targets* 2012;**11**(1):3-14.

Savarino 1993

Savarino SJ, Bourgeois AL. Diarrhoeal 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.

Schnadower 2019a

Schnadower D, Tarr PI, Freedman SB. Letter: *Lactobacillus rhamnosus* GG offers no benefit over placebo in children with acute gastroenteritis. *Alimentary Pharmacology & Therapeutics* 2019;**50**:620-2. [DOI: 10.1111/apt.15418]

Schnadower 2019b

Schnadower D, Tarr PI, Freedman SB. Letter: Lactobacillus rhamnosus GG offers no benefit over placebo in children with acute gastroenteritis. *Alimentary Pharmacology & Therapeutics* 2019;**50**:620-2. [DOI: 10.1111/apt.15418]

Sniffen 2018

Sniffen JC, McFarland LV, Evans CT, Goldstein EJC. Choosing an appropriate probiotic product for your patient: an evidence-based practical guide. *PLoS ONE* 2018;**13**(12):e0209205.

Su 2020

Su GL, Ko CW, Bercik P, Yngve Falck-Ytter, Sultan S, Weizman AV, et al. AGA Clinical Practice Guidelines on the role of probiotics in the management of gastrointestinal disorders. *Gastroenterology* 2020;**159**:697-705. [DOI: 10.1053/j.gastro.2020.05.059]

Surendran Nair 2017

Surendran Nair M, Amalaradjou MA, Venkitanarayanan K. Antivirulence properties of probiotics in combating microbial pathogenesis. *Advances in Applied Microbiology* 2017;**98**:1-29.

Szajewska 2019a

Szajewska H, Kołodziej M, Gieruszczak-Białek D, Skórka A, Ruszczyński M, Shamir R. Systematic review with meta-analysis: Lactobacillus rhamnosus GG for treating acute gastroenteritis in children – a 2019 update. *Alimentary Pharmacology & Therapeutics* 2019;**49**:1376–84.

Szajewska 2019b

Szajewska H, Kołodziej M, Shamir R. Letter: Lactobacillus rhamnosus GG offers no benefit over placebo in children with acute gastroenteritis. Authors' reply. *Alimentary Pharmacology & Therapeutics* 2019;**50**:622-3. [DOI: 10.1111/apt.15431]

UNICEF 2018

UNICEF. Diarrhoeal disease. https://data.unicef.org/topic/child-health/diarrhoeal-disease/# (accessed 24 July 2019).

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, Switzerland: World Health Organization, 1990.

WHO 2001

World Health Organization. The World Health Report : 2001: Mental Health: New Understanding, New Hope. Geneva, Switzerland: World Health Organization, 2001.

WHO 2005

Department of Child and Adolescent Health and Development. The Treatment of Diarrhoea: A Manual for Physicians and Other Senior Health Workers. Geneva, Switzerland: World Health Organization, 2005.

Williams 2010

Williams NT. Probiotics. *American Journal of Health-System Pharmacy* 2010;**67**:449-58.

Wolvers 2010

Wolvers D, Antoine JM, Myllyluoma E, Schrezenmeir J, Szajewska H, Rijkers GT. Guidance for substantiating the evidence for beneficial effects of probiotics: prevention and management of infections by probiotics. *Journal of Nutrition* 2010;**140**(3):698S-712S.

Yelin 2019

Yelin I, Flett KB, Merakou C, Mehrotra P, Stam J, Snesrud E, et al. Genomic and epidemiological evidence of bacterial transmission from probiotic capsule to blood in ICU patients. *Nature Medicine* 2019;**25**:1728-32.

References to other published versions of this review

Allen 2000

Allen SJ, Okoko B, Martinez E, Gregorio G, Dans LF. Probiotics for treating infectious diarrhoea. *Cochrane Database of Systematic Reviews* 2000, Issue 10. Art. No: CD003048. [DOI: 10.1002/14651858.CD003048]

Allen 2003

Allen SJ, Okoko B, Martinez EG, Gregorio GV, Dans LF. Probiotics for treating infectious diarrhoea. *Cochrane Database of Systematic Reviews* 2003, Issue 10. Art. No: CD003048. [DOI: 10.1002/14651858.CD003048.pub2]

Allen 2010

Allen SJ, Martinez EG, Gregorio GV, Dans LF. Probiotics for treating acute infectious diarrhoea. *Cochrane Database of Systematic Reviews* 2010, Issue 11. Art. No: CD003048. [DOI: 10.1002/14651858.CD003048.pub3]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Aggarwal 2014

Study characteristics	
Methods	Open-label randomized controlled trial; 1 centre Duration: 18 months (October 2010 to March 2012)
Participants	Inclusion criteria: aged 6 months to 5 years; presented with acute diarrhoea (less than 7 days' duration) to the outpatient department (OPD) or to paediatric emergency services Exclusion criteria: severe malnutrition (weight for height < 3 SD of WHO charts); dysentery (presence of visible blood in stools); clinical evidence of coexisting acute systemic illness (e.g. meningitis, sepsis, pneumonia); clinical evidence of chronic disease (e.g. chronic gastrointestinal disease, chronic liver disease, chronic renal disease, nephrotic syndrome); use of probiotics in the preceding 3 weeks; use of antibiotics for current episode of diarrhoea Number completing the study: 87/100* (87%) in the probiotic group (6 non-contactable, 6 discontinued intervention); 88/100* (88%) in the control group (10 non-contactable; 3 discontinued intervention). All randomized patients analysed for primary outcomes. *Numbers lost to follow-up do not add up in the paper

Aggarwal 2014 *(Continued)*

Interventions	• Lyophilized *Lactobacillus casei*, strain GG; contents of 1 capsule (Culturelle Probiotic, Amerifit, Pittsburgh, PA, USA) containing 10 billion CFUs/d, dissolved in milk, for 5 days Timing of start of administration not stated. All participants were given reduced osmolarity ORS and zinc sulphate dispersible tablets 20 mg/d for 14 days and continued feeding. Severe dehydration was managed with IV Ringer's lactate as per WHO guidelines
Outcomes	• Duration of diarrhoea (time in hours from enrolment to the last abnormal (loose or liquid) stool) • Time to change in stool consistency (evaluated on a Likert scale with improvement recorded when there was improvement by at least 1 score) • Last abnormal stool (when child passed normal stool or no stool for next 24 hours) • Number of loose stools per day during the entire episode • Duration of vomiting • Duration of hospital stay • Adverse effects No adverse events were attributed to the probiotic
Notes	Study location: India (high child and adult mortality) Cause of diarrhoea: rotavirus identified in 21/85 (24.7%) probiotic and 20/85 (23.5%) control. Bloody diarrhoea excluded Nutritional status: weight for height 86.07% (± 8.44) probiotic and 84.25% (± 10.80) control. Severe malnutrition excluded (weight for height < 3 SD of WHO charts) Hydration status: no dehydration 70 (70%) probiotic, 64 (64%) control; some dehydration 28 (28%) probiotic, 31 (31%) control; severe dehydration 2 (2%) probiotic, 5 (5%) control Source of funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomization
Allocation concealment (selection bias)	Unclear risk	Unclear method of allocation concealment. Open study – fixed block size may allow prediction of allocation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Primary outcomes reported for > 90% in both groups
Selective reporting (reporting bias)	Low risk	All pre-stated primary outcomes reported

Azim 2014

Study characteristics	
Methods	Randomized controlled trial; 1 centre Duration: 7 months (April to October 2010)
Participants	Inclusion criteria: children aged 1 to 5 years; acute diarrhoea with dehydration Exclusion criteria: severe dehydration with danger signs as defined by WHO classification for dehydration assessment; grade 3 and 4 malnutrition as defined by modified Gomez classification; dysentery; more than 2 episodes of diarrhoea in the past 2 months; any other coexisting acute systemic illness Number completing the study: 45/45 in the probiotic group (100%); 45/45 in the control group (100%)
Interventions	*Saccharomyces boulardii*, 250 mg twice daily for 5 days Timing of start of intervention not stated All participants were given oral/parenteral rehydration therapy and electrolyte replacement when needed
Outcomes	• Presence of vomiting • Presence of fever • Presence of dehydration • Stool frequency • Duration of hospitalization No adverse events attributed to probiotic
Notes	Study location: Pakistan (high child and adult mortality) Causes of diarrhoea: dysentery excluded Nutritional status: grade 3 and 4 malnutrition excluded (modified Gomez classification) Hydration status: all participants had moderate dehydration Source of funding: not stated

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Patients were divided into 2 groups by lottery method
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo used
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated

Azim 2014 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up ≥ 90% in both groups
Selective reporting (reporting bias)	Low risk	All outcomes reported

Basu 2007

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

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Basu 2007 *(Continued)*

Random sequence generation (selection bias)	Low risk	Computer randomization
Allocation concealment (selection bias)	Low risk	Opaque and sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical placebo; intervention in numbered packets
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Investigators blinded to intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up ≥ 90% in both groups
Selective reporting (reporting bias)	Low risk	All pre-stated outcomes reported

Basu 2009

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

Basu 2009 *(Continued)*

Notes	Study location: India (high child and adult mortality) Cause of diarrhoea: bacterial diarrhoea excluded. Rotavirus identified in 106 (57.0%) probiotic and 102 (55.1%) control Nutritional status: severe malnutrition in 17 (9.1%) probiotic and 12 (6.5%) control; mild/moderate malnutrition in 102 (54.8%) probiotic and 100 (54.1%) control Hydration status: severe dehydration in 35 (18.8%) probiotic and 39 (21.1%) control; mild/moderate dehydration in 121 (65.1%) probiotic and 122 (66.0%) control Source of funding not stated, but no study authors had a financial arrangement regarding this study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers
Allocation concealment (selection bias)	Low risk	Opaque, sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical placebo; intervention in numbered packets
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Investigators blinded to intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up ≥ 90% in both groups
Selective reporting (reporting bias)	Low risk	All pre-stated outcomes reported

Bhat 2018

Study characteristics

Methods	Open-label randomized controlled trial; 1 centre Duration: 2 years (2010 to 2012)
Participants	Inclusion criteria: children aged 6 months to 5 years; admitted to hospital with acute watery diarrhoea of less than or equal to 48 hours' duration Exclusion criteria: history of blood or pus in stools; severely dehydrated (WHO criteria); severely malnourished (grade III and IV according to IAP classification); treatment with antibiotics, probiotics, or prebiotics within 2 weeks before enrolment; history of conditions known to produce immunodeficiency (AIDS, other congenital immunodeficiency syndrome, drug therapy with steroids, anticancer drugs etc.); presence of acute systemic illness (meningitis, pneumonia, sepsis); chronic diarrhoea; known hypersensitivity to *Bacillus clausii* and *Saccharomyces boulardii* or other probiotics

Bhat 2018 *(Continued)*

	Number completing study: 40/40 in both probiotic groups (100%); 40/40 in control group (100%)
Interventions	• *Saccharomyces boulardii*, 250 mg twice daily; duration not stated (data extracted for probiotic group) • *Bacillus clausii*, 2 billion spores twice a day; duration not stated Timing of start of intervention not stated. All participants received oral rehydration therapy and zinc
Outcomes	• Total duration of diarrhoea after admission: hours from time of admission to time the child passed the last abnormal (loose or liquid) stool • Mean number of stools per day • Duration of vomiting • Duration of fever (> 37.5°) • Duration of hospital stay No comment regarding adverse events
Notes	Study location: India (high child and adult mortality) Cause of diarrhoea: bloody diarrhoea excluded Nutritional status: no malnutrition: 19 (47.5%), grade 1 malnutrition: 18 (45%), grade 2 malnutrition: 3 (7.5%) in *S boulardii* group; no malnutrition: 21 (52.5%), grade 1 malnutrition: 17 (42.5%), grade 2 malnutrition: 2 (5%) in *B clausii* group; no malnutrition: 24 (60.0%), grade 1 malnutrition: 14 (35.0%), grade 2 malnutrition: 2 (5%) in control group Hydration status: some dehydration in 24 (60%) in the *S boulardii* group, 29 (72.5%) in the *B clausii* group, and 22 (55.0%) in the control group. Severe dehydration excluded Source of funding: no funding sources identified

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomization not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial; no placebo
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label trial; no placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up ≥ 90% in both groups
Selective reporting (reporting bias)	Low risk	All outcomes reported

Bhatnagar 1998

Study characteristics	
Methods	Randomized controlled trial; 2 centres Duration: 16 months
Participants	Inclusion criteria: inpatients; malnourished boys aged 4 to 48 months (weight for height < 80% NCHS median) with diarrhoea (≥ 5 liquid stools in preceding 24 hours) for ≤ 96 hours. Nearly all children were dehydrated (48/49 milk group and 43/47 yogurt group) Exclusion criteria: female; severe non-gastrointestinal illness; gross blood in the stools; exclusive breast-feeding Numbers completing study: 47/49 (95.9%) in probiotic group (2 were withdrawn because of cholera in stool cultures); 49/53 (92.5%) in control group (2 were withdrawn because of cholera in stool cultures, 2 left against medical advice)
Interventions	• Yogurt formula (Lactogen-2 (Nestle India Ltd, Gurgaon, Haryana); after fermentation with 90 g *Streptococcus thermophilus* and *Lactobacillus bulgaricus* standard starter (International Yoghurt Manufacturers Club, Paris, France), 120 mL/kg/d for at least 72 hours added to milk formula) • Non-fermented Lactogen-2 Given after 8 hours' initial observation. All participants received rehydration fluids (IV if stool > 4 g/kg/h), IV cephalosporin, and gentamicin, and were fed with rice lentil oil gruel
Outcomes	• Proportion recovered at 48 hours and 72 hours (defined as 2 consecutive formed stools, ≤ 3 stools in 24 hours, of which at least 2 were formed, or no stool for 12 hours) • Median duration of diarrhoea • Treatment failure (episode of diarrhoea after 72 hours or stool weight > 150 g/kg on any day) No comment regarding adverse events
Notes	Study location: India (high child and adult mortality) Cause of diarrhoea: excluded if gross bloody stools Nutritional status: all malnourished boys (weight for height < 80% NCHS median); mean weight for length and length for age (% NHCS median) similar in both groups Hydration status: nearly all children were dehydrated: 43/47 (91.5%) probiotic and 48/49 (98.0%) control Source of funding: not stated

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Block randomization list
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Interventions not identical

Bhatnagar 1998 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear who assessed outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up ≥ 90% in both groups
Selective reporting (reporting bias)	Low risk	All pre-stated outcomes reported

Billoo 2006

Study characteristics	
Methods	Randomized trial; probably open study; 1 centre Duration: not stated
Participants	Inclusion criteria: inpatients; infants and children with acute watery diarrhoea of mild to moderate severity Exclusion criteria: severe intercurrent illness; severe diarrhoea and dehydration requiring admission and IV rehydration; temperature > 38.5° C; anti-diarrhoeals or antibiotics in last 24 hours; severe malnutrition Numbers completing study: 50/50 (100%) in probiotic group; 50/50 (100%) in control group
Interventions	• *S boulardii* (500 mg/d for 5 days) • ORF and nutritional support only Timing of interventions not stated
Outcomes	• Mean duration of diarrhoea (not defined), days: 3.6 in probiotic group, 4.8 in placebo group (P = 0.001) • Weight gain • Daily stool frequency and consistency: mean numbers of stools on days 3 and 6 were significantly lower in the probiotic group than in the placebo group • Tolerance and acceptability of intervention No adverse events attributed to probiotic
Notes	Study location: Pakistan (high child and adult mortality) Cause of diarrhoea: rotavirus identified in 8 (16.0%) probiotic and 10 (20.0%) control. Bacterial diarrhoea identified in 13 (26.0%) probiotic and 6 (12.0%) control Nutritional status: severe malnutrition excluded; no further data presented Hydration status: severe dehydration excluded; no further data presented Source of funding: supported by Laboratoires Biocedex (France); Hilton Pharma (Pvt) Ltd (Pakistan)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Billoo 2006 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Randomized controlled trial but methods not described
Allocation concealment (selection bias)	Unclear risk	Methods not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear who assessed outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up ≥ 90% in both groups
Selective reporting (reporting bias)	Low risk	All pre-stated outcomes reported

Boudraa 2001

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

Boudraa 2001 *(Continued)*

Notes	Study location: Algeria (high child and adult mortality) Cause of diarrhoea: rotavirus identified in 25/56 (44.6%) probiotic and 26/56 (46.4%) control. No bacterial pathogens isolated Nutritional status: all well nourished Hydration status: all dehydrated; severe dehydration 5 (8.9%) probiotic and 4 (7.1%) control Reduced duration of diarrhoea in probiotic compared with non-probiotic group observed only in children with reducing substances in stools Source of funding: not stated Secondary outcome reporting: outcome data presented for < 90% in both groups

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Interventions not identical
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear who assessed outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcomes reported for > 90% in both groups
Selective reporting (reporting bias)	Low risk	All pre-stated outcomes reported

Bruno 1981

Study characteristics

Methods	Randomized controlled trial; 1 centre Duration: not stated
Participants	Inclusion criteria: inpatients; adults with acute enteritis (diarrhoea, fever, vomiting, nausea, abdominal pain with or without toxicity; duration not stated) Exclusion criteria: typhoid cases Number completing study: stool cultures available after randomization; participants with *Salmonella typhi* were withdrawn (number not stated); for non-typhoid participants, results were presented for 25/25 (100%) probiotic and 24/24 (100%) control

Bruno 1981 *(Continued)*

Interventions	• *Enterococcus LAB* SF68 (Bioflorin; ≥ 75 × 10^6 lyophilized bacteria tds for 10 days) • Placebo Timing of start of administration not stated
Outcomes	• Proportion of participants with diarrhoea by day of treatment Resolution of diarrhoea defined as 2 or fewer formed stools/d and no abdominal pain or fever No adverse events attributed to probiotic
Notes	Study location: Italy (very low child and adult mortality) Cause of diarrhoea: non-typhoid. Bacterial stool culture (probiotic group/placebo group): Salmonella 4/3; enteropathogenic *E coli* 18/20; other enteropathogen 1/3 Nutritional status: no data presented Hydration status: no data presented Source of funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding not adequately described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear who assessed outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up ≥ 90% in both groups
Selective reporting (reporting bias)	Low risk	All pre-stated outcomes reported

Bruno 1983

Study characteristics

Methods	Randomized controlled trial; 1 centre Duration: not stated
Participants	Inclusion criteria: inpatients; adults (although ages not specified) with acute febrile enteritis (duration of diarrhoea not stated)

Bruno 1983 *(Continued)*

	Exclusion criteria: typhoid cases Numbers completing study: 10/10 (100%) probiotic, 11/11 (100%) control
Interventions	• *Enterococcus LAB* SF68 (Bioflorin; ≥ 75 × 10^6 lyophilized bacteria thrice daily for at least 10 days) • Placebo Intervention started after initial treatment with chloramphenicol (all participants) and after stool culture results available
Outcomes	• Proportion of participants with diarrhoea by day of treatment (definition for recovery from diarrhoea not stated) No adverse events attributed to probiotic
Notes	Study location: Italy (very low child and adult mortality) Cause of diarrhoea: non-typhoid Nutritional status: no data presented Hydration status: no data presented Source of funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomization unclear
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Placebo not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up ≥ 90% in both groups
Selective reporting (reporting bias)	Low risk	All pre-stated outcomes reported

Burande 2013

Study characteristics

Methods	Prospective, parallel, single-blind, randomized controlled trial; 1 centre Duration: 2 years (July 2009 to July 2011)

Burande 2013 *(Continued)*

Participants	Inclusion criteria: children diagnosed with acute diarrhoea (≥ 3 unformed stools in last 24 hours with duration < 48 hours); no dehydration or some dehydration as per WHO criteria Exclusion criteria: concurrent chronic illness; severe and very severe undernutrition (weight for age < 60% of 50th percentile - CDC 2000 Standards); severe dehydration (as per WHO criteria); allergy or history of use of probiotic, antibiotic, or anti-diarrhoeal in last 24 hours Numbers completing study: 35/36 (97%) probiotic (1 lost to follow-up); 35/36 (97%) control (1 lost to follow-up). Reasons for loss to follow-up not given
Interventions	• Lyophilized *Saccharomyces boulardii*, 250 mg orally twice a day for 5 days Timing of start of administration not stated. All participant children received ORS ad libitum (as much as required after passing of each stool or vomiting, or both, and whenever child demand for it) until resolution of diarrhoea, and zinc (10 mg/d if aged < 6 months and 20 mg/d if aged ≥ 6 months) for 14 days. Paracetamol was given as required for fever
Outcomes	• Recovery from diarrhoea (passage of 2 consecutive formed stools as per King scoring system or no stool for 12 hours) • Recovery from vomiting (duration in days until last episode of vomiting) or up to 14 days, whichever occurred later • Adverse events No specific comment regarding adverse events
Notes	Study location: India (high child and adult mortality) Cause of diarrhoea: *Vibrio cholerae*, *Entamoeba histolytica,* and *Giardia lamblia* excluded Nutritional status: severe undernutrition excluded (weight for age < 60% of 50th percentile - CDC 2000 Standards) Hydration status: no dehydration 32 (91.4%) probiotic, 31 (88.6%) control; some dehydration 3 (8.6%) probiotic, 4 (11.4%) control. Severe dehydration excluded Source of funding: DY Patil University, Kolhapur, and management to provide financial support

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers
Allocation concealment (selection bias)	Unclear risk	Not adequately described
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up ≥ 90% in both groups

Burande 2013 *(Continued)*

Selective reporting (reporting bias)	Low risk	All pre-stated outcomes reported

Burki 2017

Study characteristics	
Methods	Prospective randomized study; 1 centre Duration: 4 months (May to October 2016)
Participants	Inclusion criteria: children aged 6 months to 5 years, irrespective of hydration status; present or past status of use of antibiotics; ability to tolerate *Saccharomyces boulardii* Exclusion criteria: recurrent or chronic diarrhoea; acute dysentery; thalassaemia; congenital heart disease Numbers completing study: 200/234 (85.5%) both probiotic and control (21 patients prematurely discharged and 13 left against medical advice). Unclear number originally allocated to each group and from which group withdrawals came; 100 ultimately allocated to both probiotic and control groups
Interventions	• *Saccharomyces boulardii* (dose, frequency, and duration not stated; not stated whether probiotic alive or killed) Timing of start of administration not stated. All participants received 'routine management' of acute diarrhoea (not described)
Outcomes	• Stool frequency • Stool consistency • Mean duration of diarrhoea (days) No specific comment regarding adverse events
Notes	Study location: Pakistan (high child and adult mortality) Cause of diarrhoea: acute dysentery excluded Nutritional status: not stated Hydration status: mild dehydration 17 (17%) probiotic, 14 (14%) control; moderate dehydration 57 (57%) probiotic, 66 (66%) control; severe dehydration 26 (26%) probiotic, 20 (20%) control Source of funding: not stated

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not adequately described
Allocation concealment (selection bias)	High risk	Not described
Blinding of participants and personnel (performance bias)	High risk	No placebo

Burki 2017 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	High risk	Follow-up < 90%
Selective reporting (reporting bias)	Low risk	All pre-stated outcomes reported

Buydens 1996

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

Buydens 1996 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization by central computer
Allocation concealment (selection bias)	Unclear risk	No specific details of allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Identical placebo; outcomes assessed by blinded patients
Incomplete outcome data (attrition bias) All outcomes	High risk	Follow-up < 90% in both groups
Selective reporting (reporting bias)	Low risk	All pre-stated outcomes reported

Canani 2007

Study characteristics	
Methods	Randomized controlled trial; 6 centres Duration: 12 months (October 1999 to September 2000)
Participants	Inclusion criteria: outpatients; infants and children aged 3 to 36 months with > 2 loose or liquid stools/d for < 48 hours Exclusion criteria: malnutrition; severe dehydration; coexisting acute systemic illness (meningitis, sepsis, pneumonia); immunodeficiency; underlying severe chronic disease; cystic fibrosis; food allergy or other chronic GI disease; use of probiotics in the previous 3 weeks; antibiotic or any other anti-diarrhoeal medication in the previous 3 weeks; poor compliance (< 4 doses of study medication administered) Numbers completing study: 95/100 probiotic (2 did not receive allocated intervention, 1 faster remission, 1 worsening symptoms, 1 poor compliance); 88/92 control (1 did not receive allocated intervention, 1 worsening symptoms, 1 contracted pneumonia, 1 coeliac disease)
Interventions	• Live *Lactoacillus casei rhamnosus* GG (Dicoflor 60; 12×10^9 CFUs/d for 5 days) • Placebo, no details given but same appearance as active intervention Intervention started within 48 hours of admission. ORF given for 3 to 6 hours after admission, lactose-containing formula milk or cow's milk according to age
Outcomes	• Diarrhoea duration (time of last loose or liquid stool preceding a normal stool) • Number and consistency (scoring system) of stools/d recorded by parents • Vomiting

Canani 2007 *(Continued)*

- Fever (> 37.5° C)
- Number of hospital admissions

1 participant with poor compliance in the probiotic group; 31 and 34 participants with vomiting in probiotic and placebo groups, respectively. No adverse events attributed to probiotic

Notes

Study location: Italy (very low child and adult mortality)

Cause of diarrhoea: stool culture in only a few participants; no data presented

Nutritional status: malnutrition excluded

Hydration status: severe dehydration excluded; no other data presented

Source of funding: none

Single-blind trial: parents instructed to buy probiotic preparation

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

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

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization list; allocation in blocks of 6
Allocation concealment (selection bias)	Unclear risk	No specific details of allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Parents of participants told which treatment to purchase
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors blinded to intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up ≥ 90% in both groups
Selective reporting (reporting bias)	Low risk	All pre-stated outcomes reported

Cetina-Sauri 1994

Study characteristics	
Methods	Randomized controlled trial; 1 centre Duration: 11 months (1 April 1988 to 15 March 1989)
Participants	Inclusion criteria: unclear whether inpatients or outpatients, or both; children aged 3 months to 3 years with acute (duration not stated) non-bloody diarrhoea; no dehydration; no concomitant illness; no antibiotics or drugs affecting gut motility. Numbers 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	• *S boulardii* (live *Saccharomyces cerevisiae Hansen* CBS 5926; 600 mg/d; duration not stated) • Glucose placebo (diluted in 5 mL cold water) No details of when interventions started
Outcomes	• Number of stools per day • First day stools formed • Side effects Cure defined as < 4 stools in 24 hours and absence of liquid stools No adverse events attributed to probiotic
Notes	Study location: Mexico (low child and adult mortality) Cause of diarrhoea: bloody diarrhoea excluded Nutritional status: all well nourished Hydration status: dehydration excluded Source of funding: not stated

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random numbers table
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unclear whether placebo and probiotic identical
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear who assessed outcomes
Incomplete outcome data (attrition bias)	Unclear risk	Unclear how many participants were randomized at start of study

Cetina-Sauri 1994 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Unclear risk	N/A - neither primary outcome reported

Chen 2010

Study characteristics	
Methods	Randomized controlled trial; 1 centre Duration: 22 months (February 2006 to November 2007)
Participants	Inclusion criteria: inpatients; children aged 3 months to 6 years with acute diarrhoea defined as 3 or more loose or liquid stools per day of less than 72 hours' duration Exclusion criteria: immunodeficiency; severe abdominal distension with risk of bowel perforation; severe infection or sepsis; history with gastrointestinal tract surgery; use of probiotics in the preceding week Numbers completing study: 304 children enrolled and 293 were included in the analysis (150 probiotic and 143 control). Overall, 7 children discontinued medication and 4 were lost to follow-up; group allocation unclear
Interventions	• Live *Bacillus mesentericus*, *Enterococcus faecalis*, and *Clostridium butyricum* (Bio-three; 2.5×10^7 CFUs/kg/d) for 7 days • Starch powder of identical appearance to probiotic preparation When interventions were started is not stated
Outcomes	• Duration of diarrhoea (time from inclusion into the study until the first normal stool was passed) • Number of diarrhoea episodes • Mean stool frequency on days 2 and 3 • Diarrhoea lasting ≥ 3 days • Duration of fever • Duration of vomiting • Appetite/intake score • Abdominal pain episodes • Length of hospital stay Duration of diarrhoea also reported for children with rotavirus diarrhoea and those with bacterial diarrhoea No adverse events attributed to probiotic
Notes	Study location: Taiwan (low child and adult mortality) Cause of diarrhoea: 47 (31.3%) children in probiotic group and 44 (30.8%) in control group had rotavirus in stools. Norovirus and adenovirus were also identified. 27 (18.0%) children in probiotic group and 30 (20.0%) in control group had bacteria in stools (either *Salmonella enterica* or *Campylobacter jejuni*) Nutritional status: no data presented Hydration status: no data presented Source of funding: this study was supported in part by a grant from Chang Gung Memorial Hospital research project grant XMRPG440021, Northern Taiwan

Chen 2010 *(Continued)*

First author was contacted and was asked to clarify

- Whether children who had received antibiotics before recruitment were included
- Whether children with blood in stools were included
- Whether study authors could provide outcome results separately for rotavirus diarrhoea
- Hydration status
- Nutritional status

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization
Allocation concealment (selection bias)	Unclear risk	Unclear method of allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors blinded to intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up ≥ 90% in both groups
Selective reporting (reporting bias)	Low risk	Pre-stated outcomes reported

Correa 2011

Study characteristics

Methods	Double-blind randomized placebo-controlled parallel-group trial; 2 centres Duration: 18 months (April 2007 to September 2008)
Participants	Inclusion criteria: children of both sexes aged 6 to 48 months; no other diarrhoea episode or use of antibiotics 2 weeks before the trial; acute diarrhoea within 72 hours before hospitalization Exclusion criteria: exclusive breast-feeding; macroscopic blood in the faeces; severe malnutrition (weight/height < 70% National Center for Health Statistics); impossibility of oral nutrition; existence of underlying pathology (e.g. sepsis, cystic fibrosis, renal insufficiency, liver disease); children needing specific treatment Numbers completing study: 90/95 (94.7%) probiotic group (3 lost to follow-up (needed antibiotics); 2 did not complete treatment (no reason)); 86/91 (94.5%) control (2 lost to follow-up (needed antibiotics); 3 did not complete treatment (no reason given)). All randomized patients were analysed under intention-to-treat analysis

Correa 2011 *(Continued)*

Interventions	• Lyophilized *Saccharomyces boulardii*, capsules (Floratil; Merck S.A., Rio de Janeiro, Brazil) containing 200 mg of yeast (4×10^9 viable cells) and magnesium stearate, lactose, and sucrose as excipients, 12-hourly for 5 days • Placebo capsules (Faculdade de Farmácia, Universidade Federal de Goiás, Goiânia, Brazil) containing 200 mg of the excipients 12-hourly for 5 days Timing of start of administration not stated
Outcomes	• Clinical cure for diarrhoea (if no improvement after 4 days of intervention, therapy was discontinued and child was remanded for further treatment) No adverse events attributed to probiotic
Notes	Study location: Brazil (low child and adult mortality) Cause of diarrhoea: rotavirus detected in 58.5% in probiotic group and in 56.3% in control group. Bloody diarrhoea excluded Nutritional status: severe malnutrition excluded Hydration status: 88/90 (97.8%) probiotic had moderate to grave dehydration, as did 85/86 (98.8%) control Source of funding: supported by Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) and Coordenação de Aperfeiçoamento do Pessoal de Ensino Superior (CAPES)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated numbers
Allocation concealment (selection bias)	Unclear risk	Unclear method of allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors blinded to intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up ≥ 90% in both groups
Selective reporting (reporting bias)	Low risk	Pre-stated outcome reported

Costa-Ribeiro 2003

Study characteristics

Methods	Randomized controlled trial; 1 centre

Costa-Ribeiro 2003 *(Continued)*

	Duration: not stated
Participants	Inclusion criteria: inpatients; boys age 1 to 24 months with acute diarrhoea (3 or more watery or loose stools per 24 hours during at least one 24-hour period in the 72 hours before admission) with moderate dehydration or severe dehydration after correction by rapid IV fluids Exclusion criteria: systemic infection requiring antibiotic; severe malnutrition (weight for age < 65% of NCHS standards); bloody diarrhoea Numbers completing study: 61/61 (100%) probiotic and 63/63 (100%) control
Interventions	• *L casei* subspecies *rhamnosus* 10×10^9 CFUs/d • Inulin 320mg/d Interventions started after correction of severe dehydration if required
Outcomes	• Duration of diarrhoea (cessation of diarrhoea defined as passage of 2 formed or semi-formed stools or no stools for 24 hours). Note: SDs quoted for mean duration of diarrhoea in each group appeared small in comparison with other trials. Study authors contacted and clarification awaited • Diarrhoea lasting 3 days or longer • Diarrhoea lasting 4 days or longer • 24-hour and total stool output • Unscheduled IV fluids • Vomiting during first 24 hours after randomization • Hyponatraemia at 24 hours after randomization No comment regarding adverse events
Notes	Study location: Brazil (low child and adult mortality) Cause of diarrhoea: bloody diarrhoea excluded; 52% of children probiotic and 48% control had rotavirus in stools; no data shown for outcomes in rotavirus diarrhoea, although stated as "no significant difference" between groups Nutritional status: severe malnutrition excluded; median WHZ score -1.13 (IQR -1.63 to -0.43) in control group and -1.22 (-1.87 to -0.62) in probiotic group Hydration status: all dehydrated; moderate or severe dehydration in 92% probiotic and 94% control Source of funding: this study was supported in part by a grant from Pronex/CNPq (661086/1998-4), Brazil

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not adequately described
Allocation concealment (selection bias)	Unclear risk	Not adequately described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical placebo
Blinding of outcome assessment (detection bias)	Unclear risk	Unclear who assessed outcomes

Costa-Ribeiro 2003 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up ≥ 90% in both groups
Selective reporting (reporting bias)	Low risk	Pre-stated outcomes reported

D'Apuzzo 1982

Study characteristics

Methods	Randomized controlled trial; unclear whether single centre or multi-centre Duration: not stated
Participants	Inclusion criteria: unclear whether inpatients or outpatients, or both; children with acute enteritis (duration and definition not given) Exclusion criteria: none stated Numbers completing study: 21/21 (100%) probiotic and 18/18 (100%) control
Interventions	• Live *Streptococcus faecium* (*S faecium* 68; 75 × 10^6 bacteria thrice daily for 7 days) • Placebo (details not given) When interventions started is not stated
Outcomes	• Number of participants with < 2 stools/d • Formed yellow/brown stools without mucus • No abdominal pain, vomiting, or fever for the whole day No adverse events attributed to probiotic
Notes	Study location: Switzerland (very low child and adult mortality) Cause of diarrhoea: 7 participants in each group had positive stool culture for bacteria Nutritional status: no data presented Hydration status: no data presented *S faecium* 68 also appeared to promote recovery from abdominal pain, fever, and vomiting Source of funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described

D'Apuzzo 1982 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not adequately described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not adequately described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up ≥ 90% in both groups
Selective reporting (reporting bias)	Low risk	Pre-stated outcome reported

Dalgic 2011

Study characteristics	
Methods	Prospective randomized single-blind controlled trial; 1 centre Duration: 22 months (September 2008 to June 2010)
Participants	Inclusion criteria: time between onset of diarrhoea and hospitalization < 96 hours; presenting with an episode of 3 or more watery or looser-than-normal stools within a 24-hour period and/or forceful vomiting (excluding post-tussive vomiting); mild to moderate dehydration; on admission, stool positive for rotavirus antigen Exclusion criteria: malnutrition as judged by the ratio of weight to height; duration of diarrhoea > 96 hours; severe dehydration; exclusively breast-feeding; toxic clinical appearance; immunosuppression; any known allergies to any drugs or foods Numbers completing study: 60/60 (100%) probiotic plus zinc; 60/60 (100%) zinc only
Interventions	• *Saccharomyces boulardii* • Zinc (data extracted for control group) • Lactose-free formula • *Saccharomyces boulardii* and zinc (data extracted for probiotic group) • *Saccharomyces boulardii* and lactose-free formula • Zinc and lactose-free formula • *Saccharomyces boulardii*, zinc, and lactose-free formula • ORS and/or IV rehydration only *Saccharomyces boulardii*: 250 mg once daily, for a minimum of 5 days (not stated whether probiotic alive or killed) Zinc: zinc acetate suspension, 10 mg twice daily for infants < 6 months of age; 20 mg daily for all other participants Lactose-free formula: Bebelac Lactose Free Formula, 400 g; Nutricia, Istanbul, Turkey Intervention started directly after randomization. All participants offered ORS for rehydration, with IV rehydration given if excessive vomiting or clinical signs of dehydration
Outcomes	• Duration of diarrhoea • Number of vomiting episodes

Dalgic 2011 *(Continued)*

	• Number of bowel movements • Rectal temperature • Days of hospitalization No adverse events attributed to probiotic
Notes	Study location: Turkey (low child and adult mortality) Cause of diarrhoea: all patients had rotavirus diarrhoea Nutritional status: severe malnutrition excluded (Z score ≤ -3) Hydration status: mild dehydration in 7.7% probiotic plus zinc and in 8.5% zinc only; moderate dehydration in 4.8% probiotic plus zinc and in 4% zinc only. Severe dehydration excluded Source of funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not adequately described
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Different treatments given in each arm
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not adequately described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up ≥ 90% in both groups
Selective reporting (reporting bias)	Low risk	Pre-stated outcome reported

Das 2016

Study characteristics

Methods	Double-blind randomized controlled trial; 1 centre Duration: 17 months (November 2007 to March 2009)
Participants	Inclusion criteria: children with acute rotavirus diarrhoea of < 48 hours' duration; moderate to severe dehydration; aged between 3 months and 5 years Exclusion criteria: severe malnutrition (weight for height < 3 SD of WHO growth chart); coexisting systemic illness and chronic disease; taking probiotics including during preceding week; taking antibiotics for current episode of diarrhoea; history of receiving rotavirus vaccine

Das 2016 *(Continued)*

	Numbers completing study: 30/30 (100%) probiotic; 28/30 (93.3%) control (2 non-contactable). All randomized participants analysed under intention-to-treat analysis
Interventions	• Lyophilized *Saccharomyces boulardii* (Econorm, Dr Reddy's Laboratories), 250 mg mixed in 15 mL normal water, twice daily for 5 days • Control: 'similar product' in colour and taste, twice daily for 5 days Intervention started after participant was clinically stabilized and maintained hydration and randomization. All cases managed as per WHO guidelines for management of acute diarrhoea (details not given). Carers advised to avoid any warm/hot food within 2 hours of giving probiotics
Outcomes	• Duration (hours) of acute diarrhoea • Duration (hours) of vomiting • Duration (hours) of fever • Duration (hours) of hospitalization • Proportion of children requiring parenteral rehydration • Proportion of children having diarrhoea lasting beyond day 7 • Any adverse effects No adverse events attributed to probiotic
Notes	Study location: India (high child and adult mortality) Cause of diarrhoea: rotavirus detected in 100% of participants in probiotic and control groups Nutritional status: severe malnutrition excluded Hydration status: no dehydration in 14 (46.7%) probiotic and in 15 (50%) control; some dehydration in 8 (26.7%) probiotic and in 7 (23.3%) control Source of funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not adequately described
Allocation concealment (selection bias)	Low risk	Serially numbered opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unclear whether different advice given for both arms
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not adequately described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up ≥ 90% in both groups
Selective reporting (reporting bias)	Low risk	Pre-stated outcomes reported

Dinleyici 2014

Study characteristics	
Methods	Randomized single-blind parallel-group controlled trial; 11 centres Duration: not stated
Participants	Inclusion criteria: children aged 3 to 60 months; acute watery diarrhoea lasting 12 to 72 hours; hospitalized in 1 of 11 Turkish centres; clinical signs of mild to moderate dehydration (prolonged capillary refill time, abnormal skin turgor, and 3% to 9% loss of body weight) Exclusion criteria: clinical features of hypovolaemic shock and/or necessitating admission to intensive care unit; use of antibiotics or probiotics up to 1 month before admission; malnutrition (weight < P3); chronic underlying disease, including immunocompromised condition Numbers completing study: 64/70 (91.4%) probiotic (3 antibiotic prescriptions (post randomization); 1 parental refusal to continue; 2 lack of data after hospital discharge (lack of parental compliance)); 63/70 (90%) control (3 antibiotic prescriptions (post randomization); 1 parental refusal to continue; 1 detection of underlying disease during hospitalization; 1 lack of data after hospital discharge (lack of parental compliance); 1 unaccounted for)
Interventions	• *Lactobacillus reuteri* DSM 17938 (BioGaia drops, BioGaia AB, Sweden; distributed by Eczacibasi in Turkey) 1×10^8 CFUs daily for 5 days (not stated whether probiotic alive or killed) Intervention administered after randomization. All participants received hypo-osmolar ORS and/or IV therapy
Outcomes	• Duration of diarrhoea (time in hours from admission until cessation of diarrhoea - time when first normal stool was recorded (according to Bristol score; a score < 5 is described as normalization of stool) • Duration of hospitalization (days) • Number of children with diarrhoea at each day of intervention • Mean frequency of daily stools • Percentage of prolonged diarrhoea (presence of diarrhoea 7 days after intervention) • Adverse events • Length of hospitalization (days from admission until discharge) No adverse events attributed to probiotic
Notes	Study location: Turkey (low child and adult mortality) Cause of diarrhoea: bloody diarrhoea excluded Nutritional status: malnutrition excluded Hydration status: hypovolaemic shock excluded Source of funding: no funding; free medication provided (unclear from whom)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomization
Allocation concealment (selection bias)	Unclear risk	No specific details of allocation concealment

Dinleyici 2014 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessor blinded to intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up ≥ 90% in both groups
Selective reporting (reporting bias)	Low risk	Pre-stated outcome reported

Dinleyici 2015a

Study characteristics	
Methods	Randomized single-blind case-control trial; number of centres not stated Duration: not stated
Participants	Inclusion criteria: age 3 to 60 months; acute infectious diarrhoea (passage of 3 or more loose or watery stools per day) lasting 12 to 72 hours before presentation at the outpatient clinic; followed up with ambulatory care Exclusion criteria: need for hospitalization; use of antibiotics or probiotics for 1 month before a new episode of diarrhoea; severe malnutrition; severe chronic underlying disease, including immunocompromising conditions Numbers completing study: 29/32 (90.6%) probiotic (3 discontinued intervention (antibiotic prescription)); 31/32 (96.9%) control (1 discontinued intervention (antibiotic prescription))
Interventions	• *Lactobacillus reuteri* DSM 17938 (BioGaia®, Stockholm, Sweden) 5 drops containing 1×10^8 CFUs daily for 5 days (not stated whether probiotic alive or killed) Timing of start of administration not stated. All participants received hypo-osmolar ORS
Outcomes	• Duration of diarrhoea (hours) • Number of children with diarrhoea at each day of the 5 days of intervention • Adverse events No adverse events attributed to probiotic
Notes	Study location: Turkey (low child and adult mortality) Cause of diarrhoea: acute watery diarrhoea. No comment regarding specific cause of diarrhoea Nutritional status: severe malnutrition excluded Hydration status: not stated Source of funding: not stated
Risk of bias	

Dinleyici 2015a *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up ≥ 90% in both groups
Selective reporting (reporting bias)	Low risk	Pre-stated outcome reported

Dinleyici 2015b

Study characteristics	
Methods	Prospective single-blind randomized controlled trial; 8 centres Duration: not stated
Participants	Inclusion criteria: hospitalized and ambulatory children aged 3 to 60 months (ECU and outpatients); acute watery diarrhoea lasting 12 to 72 hours; clinical signs of mild to moderate dehydration (prolonged capillary refill time, abnormal skin turgor, and percentage loss of body weight) Exclusion criteria: use of antibiotics or probiotics up to 1 month before admission; malnutrition (weight under the third percentile); chronic underlying disease including immunocompromised condition. For hospitalized children, also clinical features of hypovolaemic shock, and/or need for ICU admission Numbers completing study: 220/240 (91.7%) (148/160 hospitalized; 72/80 ambulatory) probiotic (hospitalized: 2 had had antibiotics, 2 discontinued intervention as needed antibiotics, 8 were lost to follow-up; ambulatory: 3 had had antibiotics, 5 were lost to follow-up); 143/160 (89.4%) (72/80 hospitalized; 71/80 ambulatory) control (hospitalized: 3 had had antibiotics, 5 were lost to follow-up; ambulatory: 4 had had antibiotics, 3 discontinued intervention due to antibiotics, 2 were lost to follow-up). NB combined results of all participants in probiotic groups used in analyses
Interventions	• Lyophilized *Saccharomyces boulardii* CNCM 1-745 (Reflor Sachet, Biocodex, Gentilly, France) 250 mg (5×10^9 CFUs) twice daily for 5 days Timing of start of administration not stated. All participants received ORS and/or IV therapy
Outcomes	• Duration of diarrhoea (time in hours from admission until cessation of diarrhoea) • Duration of hospitalization (days) • Number of children with diarrhoea at each of the 5 days of intervention • Adverse events

Dinleyici 2015b *(Continued)*

	• Frequency and consistency of stool No adverse events attributed to probiotic
Notes	Study location: Turkey (low child and adult mortality) Cause of diarrhoea: acute watery diarrhoea. No comment regarding specific cause of diarrhoea Nutritional status: malnutrition excluded Hydration status: hypovolaemic shock excluded Source of funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization
Allocation concealment (selection bias)	Unclear risk	No specific details of allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessor blinded to intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	Overall follow-up ≥ 90%; no marked differences between arms
Selective reporting (reporting bias)	Low risk	Pre-stated outcome reported

Dubey 2008

Study characteristics

Methods	Randomized controlled trial; 1 centre Duration: February 2005 to February 2007
Participants	Inclusion criteria: inpatients; infants and children with watery diarrhoea (defined as watery stools) < 72 hours' duration due to rotavirus infection; parental consent Exclusion criteria: systemic infection; chronic disease; body weight < 60% NCHS standard; vomiting; need for antibiotics Numbers completing study: 113/113 (100%) probiotic and 111/111 (100%) control. Six children did not complete the study; no group allocation reported or reasons given

Dubey 2008 *(Continued)*

Interventions	• *L acidophilus, L paracasei, L bulgaricus, L plantarum, B breve, B infantis, B longum, S thermophilus* (VSL#3; body weight < 5 kg: 180 billion organisms/d; body weight 5 to 10 kg: 360 × 10^9 organisms/d for 4 days) • Placebo (details not given although placed in identical sachets) When interventions were started is not stated
Outcomes	Significantly lower mean stool frequency seen in probiotic group from days 2 to 4; otherwise results between groups comparable. Significantly improved stool consistency in probiotic group on day 2. Probiotic group received significantly smaller volume of ORS on days 2 and 3 Overall recovery rate was better in the probiotic group (89.4% vs 39.6%; P < 0.001) No adverse effects were attributed to probiotic
Notes	Study location: India (high child and high adult mortality) Cause of diarrhoea: all rotavirus Nutritional status: severe malnutrition excluded; statement: "malnutrition status similar in two groups" Hydration status: dehydration status similar in 2 groups at baseline but no data presented Source of funding: supported by grant from VSL Secondary outcome reporting: all pre-stated outcomes reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical interventions; participants and personnel unaware of assignment to arms
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not adequately described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up ≥ 90% in both groups
Selective reporting (reporting bias)	High risk	Primary outcome not reported in results

Dutta 2011

Study characteristics

Dutta 2011 *(Continued)*

Methods	Double-blind randomized placebo-controlled trial; 1 centre Duration: 23 months (September 2003 to July 2005)
Participants	Inclusion criteria: boys (for ease of collection of stool and urine separately); aged 6 to 24 months; suffering from dehydrating acute watery diarrhoea of less than 3 days' duration; clinical signs and symptoms of 'some' dehydration (thirst or eagerness to drink, sunken eyes, dry mouth and tongue, loss of skin elasticity) Exclusion criteria: history of an episode of diarrhoea within 1 month of the present illness to exclude recurrent and persistent diarrhoea; exclusively breast-fed; severe dehydration; diarrhoea associated with another systemic illness (e.g. septicaemia, pneumonia, urinary tract infection, otitis media) or chronic underlying disease (e.g. tuberculosis, liver disease); severe malnutrition; needing extensive care (e.g. life support system, blood transfusion, total parental nutrition); received an antibiotic before enrolment Numbers completing study: 78/80 (97.5%) probiotic (2 discontinued intervention due to unwillingness of parents); 70/80 (87.5%) control (10 discontinued intervention due to unwillingness of parents)
Interventions	• *Lactobacillus* sporogenes (*Bacillus coagulans*) (M/S ESKAG Pharma Private Limited, Kolkata, India) 2 tablets (60 million spores/tablet) dispersed in 15 mL water, twice daily until recovery/for 5 days if not recovered before that (not stated whether probiotic alive or killed) • Placebo (M/S ESKAG Pharma Private Limited, Kolkata, India) identical in colour, shape, and size Timing of start of administration not stated. All participants received reduced osmolar ORS solution to correct initial dehydration and continued as maintenance; more fluid and/or plain water if wanted/clinical indication; IV Ringer's lactate for severe dehydration/intractable vomiting. Participants allowed to continue breast-feeding, formula feeding, animal milk, or normal diet
Outcomes	• Cure rate • Duration of diarrhoea • Stool frequency • Volume of diarrhoea • Intake of ORS • Liquid/plain water intake No adverse events attributed to probiotic
Notes	Study location: India (high child and adult mortality) Cause of diarrhoea: rotavirus detected in 25 (32%) probiotic and in 26 (37.1%) control. A range of other pathogens were detected less commonly, including *V cholerae, Shigella* spp, *E coli*, astrovirus and *Cryptosporidium*. No pathogens were identified in 18 (23.1%) probiotic and in 17 (24.3%) control Nutritional status: severe malnutrition excluded Hydration status: severe dehydration excluded Source of funding: supported by the Indian Council of Medical Research (ICMR) as intramural project of National Institute of Cholera and Enteric Diseases, Kolkata, India

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers

Dutta 2011 *(Continued)*

Allocation concealment (selection bias)	Low risk	Interventions kept in coded blister foil, externally prepared
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors blinded to intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	Overall follow-up ≥ 90%; no marked differences between arms
Selective reporting (reporting bias)	Low risk	Pre-stated outcomes reported

El-Soud 2015

Study characteristics	
Methods	Prospective double-blind randomized study; 1 centre Duration: 3 months (July to September 2014)
Participants	Inclusion criteria: aged 1 to 23 months; acute diarrhoea due to gastroenteritis Exclusion criteria: severe malnutrition (weight for height < 3 SD of WHO charts); dysentery; clinical evidence of coexisting acute systemic illness (e.g. meningitis, sepsis, pneumonia); clinical evidence of chronic disease (e.g. chronic gastrointestinal disease, chronic liver disease, chronic renal disease); probiotics used in the preceding 4 weeks; antibiotics used for current episode of diarrhoea; severe dehydration Numbers completing study: 25/25 (100%) probiotic; 25/25 (100%) control
Interventions	• *Bifidobacterium lactis* 14.5 × 10^6 CFUs/100 mL supplemented into milk formula, daily for 7 days (not stated whether probiotic alive or killed) Timing of start of administration is not stated. All participants received usual treatment according to WHO guidelines and milk formula
Outcomes	• Frequency of diarrhoea • Duration of diarrhoea • Duration of hospital stay • Duration of fever • Vomiting episodes • Safety and tolerance No adverse events are attributed to probiotic
Notes	Study location: Egypt (low child and adult mortality) Cause of diarrhoea: dysentery excluded. Rotavirus detected in 66% of participants. No samples were positive for routine bacterial culture

El-Soud 2015 *(Continued)*

	Nutritional status: severe malnutrition excluded Hydration status: severe dehydration excluded Source of funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not adequately described
Allocation concealment (selection bias)	Low risk	Serially numbered, sealed opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear who assessed outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up ≥ 90% in both groups
Selective reporting (reporting bias)	Low risk	Pre-stated outcome reported

Erdogan 2012

Study characteristics

Methods	Randomized controlled trial; 1 centre Duration: 8 months (October 2009 to May 2010)
Participants	Inclusion criteria: children aged 5 months to 5 years; admitted to Bezmialem Hospital Pediatric Emergency Department with 3 or more episodes of watery diarrhoea per day in the last 48 hours; diagnosed as rotavirus gastroenteritis Exclusion criteria: severe dehydration; stool tests and microscopic examination positive for bacterial pathogens Numbers completing study: 25/25 (100%) in both probiotic groups; 25/25 (100%) in control group
Interventions	• *Saccharomyces boulardii* (spp I-745, Reflor Sache, Biocodex, Gentilly, France), 282.5 mg/d; duration not stated (data extracted for probiotic group) • *Bifidobacterium lactis* (spp B94, culture number: N◦118529, Maflor Sache, Mamsel), 30 mg/d; duration not stated Treatment start following detection of rotavirus antigen All participants received oral rehydration therapy and rapid refeeding with a normal diet

Erdogan 2012 *(Continued)*

Outcomes	• Mean duration of diarrhoea • Proportion vomiting by day No comment regarding adverse events
Notes	Study location: Turkey (low child and adult mortality) Cause of diarrhoea: all participants positive for rotavirus antigen Nutritional status: not stated Hydration status: dehydration < 5%: 12 (48%), 5% to 10%: 13 (52%) in *S boulardii* group; < 5%: 14 (44%), 5% to 10%: 11 (56%) in *B lactis* group; < 5%: 13 (52%), 5% to 10%: 12 (48%) in control group Source of funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomization not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No mention of who assessed outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up ≥ 90% in both groups
Selective reporting (reporting bias)	Low risk	All outcomes reported

Francavilla 2012

Study characteristics

Methods	Randomized double-blind placebo-controlled trial; 3 centres Duration: 7 months (January to July 2009)
Participants	Inclusion criteria: aged 6 to 36 months; hospitalized with acute diarrhoea (no longer than 7 days); clinical signs of mild to moderate dehydration (prolonged capillary refill time, abnormal skin turgor, percentage loss of body weight); no features of hypovolaemic shock Exclusion criteria: underlying chronic disease; bloody stools at the moment of first examination; current use of antibiotic/probiotic/anti-diarrhoeal medication; demonstration of a bacterial cause for diarrhoea; need for parenteral rehydration

Francavilla 2012 *(Continued)*

	Numbers completing study: 35/37 (94.6%) probiotic (2 parental non-compliance); 34/37 (91.9%) control (2 protocol deviation; 1 parental non-compliance)
Interventions	• Live *Lactobacillus reuteri* DSM 17938 (NOOS, Rome, Italy; Biogaia, Stockholm, Sweden) 5 drops twice daily (4×10^8 CFUs/d) for 7 days • Placebo (NOOS, Rome, Italy; Biogaia, Stockholm, Sweden), 5 drops twice daily Intervention started immediately after informed consent given. All participants received ORS to correct dehydration
Outcomes	• Rate of unresolved diarrhoea after 3 days of treatment (proportion of patients in each study group with continuing diarrhoea) • Duration of diarrhoea (time in hours from admission until cessation of diarrhoea) • Duration of hospitalization (time in hours from admission until discharge from hospital) • Total intake of oral rehydration solution (volume of ORS taken from admission until cessation of diarrhoea expressed in millilitres per kilogram of body weight) No adverse events attributed to probiotic
Notes	Study location: Italy (very low child and adult mortality) Cause of diarrhoea: rotavirus detected in 22/37 (59.5%) in both probiotic and control groups; adenovirus detected in 6 (16.2%) in the probiotic group and in 5 (13.5%) in the control group; no pathogens identified in 9 (24.3%) in the probiotic group and in 10 (27%) in the control group. Bloody diarrhoea excluded. Bacterial cause of diarrhoea excluded Nutritional status: not stated Hydration status: mild dehydration 25/37 (67.6%) probiotic and 26/37 (70.3%) control; moderate dehydration in 12/37 (32.4%) in the probiotic group and in 11/37 (29.7%) in the control group. No participants in either group had severe dehydration Source of funding: no funding interests to declare Discrepancy between data in text and tables for proportion of participants with ongoing diarrhoea at 48 hours; data not used. There was no statistically significant difference in duration of hospital stay between groups, but no data were presented

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessor blinded to intervention; code revealed after study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up ≥ 90% in both groups

Francavilla 2012 *(Continued)*

Selective reporting (reporting bias)	Low risk	Pre-stated outcomes reported

Freedman 2015

Study characteristics	
Methods	Prospective double-blind randomized placebo-controlled trial; 3 centres Duration: 4 years, 5 months (April 2009 to September 2013)
Participants	Inclusion criteria: aged 4 to 48 months; attended day care (≥ 2 half-days (2.5 hours/d per week attendance) at a day care centre or at home or in someone else's home, where there are, on average, ≥ 3 children including the index child); diagnosed by supervising physician as having gastroenteritis; alternative diagnostic terminologies (e.g. viral illness, diarrhoea, vomiting, viral infection) that reflect a similar diagnosis were acceptable; duration of vomiting or diarrhoea < 96 hours Exclusion criteria: if they (or a family member living in the house) had an indwelling vascular access line or congenital heart disease, were taking immunosuppressive therapy, or had a known immunodeficiency disorder; oral or gastrointestinal surgery within the preceding 7 days; pancreatic dysfunction; bloody diarrhoea; chronic gastrointestinal disease (not including constipation, irritable bowel syndrome, gastroesophageal reflux); short bowel syndrome; undergoing radiation therapy; bilious or bloody vomitus; previous enrolment in the trial; inability to speak or read English or French; supplemental probiotics in the form of powder or pill; exclusively breast-fed Numbers completing study: high dose: 30/32 (93.8%), low dose: 31/34 (91.2%) in the probiotics group (5 lost to follow-up); 62/66 (93.9%) in the control group (4 lost to follow-up)
Interventions	• Probiotic preparation of live *Lactobacillus* (*L helveticus* Rosell-52 (5%) and *L rhamnosus* Rosell-11 (95%)) along with maltodextrin, magnesium stearate, and ascorbic acid; 1 active sachet (4×10^9 viable colony forming units (CFUs) per sachet) BD for 5 days • Probiotic preparation of live *Lactobacillus* (*L helveticus* Rosell-52 (5%) and *L rhamnosus* Rosell-11 (95%)) along with maltodextrin, magnesium stearate, and ascorbic acid; 1 active sachet every morning along with a placebo sachet every night for 5 days • Placebo containing only inert excipients; identical in appearance, taste, texture, and smell Intervention was started immediately in the emergency department. All participant caregivers were instructed to give ORS and to continue normal meals. All interventions were manufactured by Institut Rosell Inc (Montreal, Quebec, Canada) NB combined results of both probiotics groups used in analyses
Outcomes	• Proportion of children missing at least 1 full day of day care related to vomiting, diarrhoea, dehydration, fever, or fluid refusal, within 2 weeks of randomization • Symptoms (e.g. vomiting, diarrhoea) that persisted into weekend days • Unscheduled visits to healthcare provider related to vomiting, diarrhoea, dehydration, fever, or fluid refusal, within 2 weeks • Subsequent hospital visit at which time IV rehydration fluids were administered within 2 weeks of randomization • Duration of vomiting and diarrhoea (time from treatment initiation until last diarrhoeal stool or episode of vomiting) • Numbers of days of day care and work absenteeism • Side effects Side effects including abdominal cramps and rash recorded for both groups; frequency of side effects higher in control group. No serious adverse events attributed to probiotic

Freedman 2015 *(Continued)*

Notes	Study location: Canada (very low child and adult mortality) Cause of diarrhoea: 39 (30%) had stools tested for viruses; rotavirus detected in 9/18 (50%) probiotic and in 12 (57%) control; adenovirus detected in 2 (11%) probiotic and in 1 (5%)control; no common bacterial pathogens detected in either group. Bloody diarrhoea excluded Nutritional status: not stated Hydration status: baseline clinical dehydration scale score (mean ± SD) 1.6 ± 1.7 probiotic and 1.3 ± 1.7 control Source of funding: funding to conduct the study provided to Stephen Freedman by Institut Rosell Lallemand Inc, which also provided study drug and placebo. Philip Sherman is the recipient of a Canada Research Chair in Gastrointestinal Disease

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization
Allocation concealment (selection bias)	Low risk	Externally generated allocation sequence
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors blinded to intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up ≥ 90% in both groups
Selective reporting (reporting bias)	Low risk	Pre-stated outcome reported

Freedman 2018a

Study characteristics

Methods	Double-blind randomized placebo-controlled trial; 6 centres Duration: 4 years, 5 months (November 2013 to April 2017)
Participants	Inclusion criteria: aged 3 to 48 months; 3 or more episodes of watery stools in a 24-hour period; vomiting or diarrhoea for less than 72 hours; clinical diagnosis of acute intestinal infection Exclusion criteria: they or person living in their household having an indwelling vascular access catheter; structural heart disease; immunocompromised or receiving immunosuppressive therapy; hematochezia; bilious vomiting; chronic gastrointestinal disorder; pancreatic dysfunction or insufficiency; use of probiotics during the preceding 14 days; allergy to soy; inability to complete follow-up; undergone oral or gastrointestinal surgery within preceding 7 days; previously participated in the trial

Freedman 2018a *(Continued)*

	Numbers completing the study: 414/444 (93%) probiotics (18 lost to follow-up, 12 withdrew) and 413/442 (93%) control (10 lost to follow-up, 19 withdrew)
Interventions	• Lyophilized powder of *L rhamnosus* R0011 and *L helveticus* R0052 (Lallemand Health Solutions) in a 95:5 ratio; 4×10^9 CFUs twice daily for 5 days • Placebo (Lallemand Health Solutions) twice daily for 5 days Participants given IV fluids as needed
Outcomes	• Modified Vesikari scale symptom score • Duration of diarrhoea and vomiting • Unscheduled physician visits • Adverse events • Number of repeat visits to the ED • Intravenous rehydration • Hospitalization • Number of days of work missed by parents or guardians • Number of days of day care missed by participants Adverse events were reported in 144 (34.8%) probiotics and in 160 (38.7%) placebo; 2 (0.5%) in the placebo group had serious adverse events
Notes	Study location: Canada (very low child and adult mortality) Cause of diarrhoea: of those who had a stool sample tested (432 probiotic and 428 placebo), 124 (28.7%) and 85 (19.9%) had rotavirus A detected, 102 (23.6%) and 124 (29.0%) had norovirus GI/GII detected, 50 (11.6%) and 45 (10.5%) had adenovirus 40/41 detected, 51 (11.8%) and 61 (14.3%) had *Clostridium difficile* toxon A/B detected, and 11 (2.6%) and 9 (2.1%) had *Salmonella* detected in probiotic and placebo groups, respectively Nutritional status: not stated Hydration status: median clinical dehydration scale score (IQR): 1 (0 to 2) probiotic and 0 (0 to 2) placebo Source of funding: Canadian Institutes of Health Research (grants 286384 and 325412), Alberta Children's Hospital Foundation Professorship in Child Health and Wellness (to Dr Freedman), grant from the Alberta Children's Hospital Foundation to the Pediatric Emergency Medicine Research Associates' Program, Calgary Laboratory Services (in kind), Provincial Laboratory for Public Health–Alberta Public Laboratories, Luminex, and Copan Italia. Dr Sherman reports receiving fees for continuing medical education from Abbott Nutrition, advisory board fees from Mead Johnson Nutritionals, fees for attending a workshop from Nestlé Nutrition Institute, and grant support from Lallemand Health Solutions and Bio-K Plus International

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number-generating software used
Allocation concealment (selection bias)	Low risk	Assignment sequence restricted to research pharmacy at the co-ordinating centre and www.randomize.net until databases were locked
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind trial: participants and all staff unaware of allocations

Freedman 2018a *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind trial: participants and all staff unaware of allocations
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up ≥ 90% in both groups
Selective reporting (reporting bias)	Low risk	Pre-stated outcomes reported

Guandalini 2000

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

Guandalini 2000 *(Continued)*

Source of funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not adequately described
Allocation concealment (selection bias)	Unclear risk	Not adequately described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Allocation code broken after study completion
Incomplete outcome data (attrition bias) All outcomes	High risk	Unclear whether withdrawals occurred at participating centres; 36/323 (11.2%) participant data forms received at the co-ordinating centre were not analysed as incomplete and/or not compliant with protocol
Selective reporting (reporting bias)	Low risk	Pre-stated outcome reported

Guarino 1997

Study characteristics

Methods	Randomized controlled trial; 1 centre Duration: 3 months (November 1995 to January 1996)
Participants	Inclusion criteria: consecutive outpatients attending 3 family physicians; infants and children with ≥ 3 watery stools/d of < 48 hours' duration Exclusion criteria: antibiotic treatment in preceding 3 weeks, breast-feeding, weight:height ratio < 5th percentile Numbers completing study: 52/52 (100%) probiotic and 48/48 (100%) control
Interventions	• Lyophilized *L casei* strain GG (Dicloflor 30; 6×10^9 million CFUs/d for maximum 5 days) re-suspended in milk or formula feed • ORF only Interventions started after 6 hours of ORF
Outcomes	• Mean duration of diarrhoea (time to last loose or liquid stool assessed by mothers) Results for rotavirus subgroup also presented No comment regarding adverse events
Notes	Study location: Italy (very low child and adult mortality) Cause of diarrhoea: rotavirus identified in 30 (57.7%) probiotic and 31 (64.6%) control

Guarino 1997 *(Continued)*

	Nutritional status: weight:height ratio < 5th percentile excluded Hydration status: all had mild to moderate dehydration Study author clarified that Figure 5 in the published article reports mean and standard error for duration of diarrhoea; SDs derived from graph. We also extracted data from Canani 1997 (abstract), which reports standard errors Probiotic also reduced prevalence of rotavirus in stools on day 6 Source of funding: Ministero della Sanità, AIDS Project (9205.30)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random numbers table
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcome assessed by participant's parent, who was aware of intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up ≥ 90% in both groups
Selective reporting (reporting bias)	Low risk	Pre-stated outcome reported

Hamid 2019

Study characteristics

Methods	Single-blind randomized controlled trial; 1 centre Duration: 1 year (March 2017 to February 2018)
Participants	Inclusion criteria: previously healthy children aged 6 months to 6 years; acute watery diarrhoea Exclusion criteria: shock; dysentery; chronic diarrhoea; other acute systemic illness; severe malnutrition and/or immunosuppressive state; use of probiotic or antibiotic in previous 3 weeks Numbers completing study: 160/160 (100%) probiotic; 150/150 (100%) control
Interventions	• *Bacillus clausii*, 2 billion spores given 12-hourly for 5 days Timing of start of intervention not stated

Hamid 2019 *(Continued)*

	All participants received oral rehydration solution, intravenous fluid as indicated, and zinc supplementation
Outcomes	• Duration of diarrhoea • Frequency of diarrhoea • Duration of hospital stay No comment regarding adverse events
Notes	Study location: Bangladesh (high child and adult mortality) Cause of diarrhoea: dysentery excluded Nutritional status: grade 1 malnutrition 48 (30%), grade 2 malnutrition 22 (14%) in probiotic group; grade 1 malnutrition 42 (28%), grade 2 malnutrition 30 (20%) in control group Hydration status: some dehydration 108 (72%), severe dehydration 29 (19%) in probiotic group; some dehydration 114 (71%), severe dehydration 33 (21%) in control group Source of funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomization not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo
Blinding of outcome assessment (detection bias) All outcomes	High risk	Single-blind study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up ≥ 90% in both groups
Selective reporting (reporting bias)	Low risk	All outcomes reported

Hegar 2015

Study characteristics

Methods	Randomized double-blind placebo-controlled prospective trial; 1 centre Duration: 5 months (January to May 2012)
Participants	Inclusion criteria: acute diarrhoea (defined as (semi-) watery stools according to Bristol criteria > type 4 lasting 48 hours or less; mild to moderate dehydration; minimum level of parental education was junior high school

Hegar 2015 *(Continued)*

	Exclusion criteria: malnutrition (weight < P3); administration of zinc; chronic condition (such as known chronic intestinal disease, cystic fibrosis, food allergy, immune deficiency, inflammatory bowel disease, GI malformation, abnormal GI motility); acute condition (antibiotic treatment during previous 7 days, macroscopic blood in the faeces, use of probiotics except for the probiotics present in infant formula) Numbers completing the study: 56/56 (100%) probiotic; 56/56 (100%) control
Interventions	• *Lactobacillus rhamnosus* R0011 1.9×10^9 and *Lactobacillus acidophilus* R0052 0.1×10^9 CFUs/d (Lacidofil®, Institute Rossel Inc, Canada, Dexa Meda, Indonesia) for 7 days (not stated whether probiotics alive or killed) • Placebo, identical capsule Timing of start of administration not stated. All participants given ORS (Indoralite®) ad libitum, 20 mg zinc sulphate/d for 10 days and normal food intake after initial rehydration
Outcomes	• Median (IQR) diarrhoea duration (hours): 68.5 (13 to 165) in probiotic group, 61.5 (21 to 166) in placebo group (P = 0.596) • Median (IQR) frequency of defecation episodes: 5.0 (0 to 23) in probiotic group, 5.5 (0 to 29) in placebo group (P = 0.795) *Outcomes not stated in methods, but given in results No adverse events attributed to probiotic
Notes	Study location: Indonesia (low child and adult mortality) Cause of diarrhoea: bloody diarrhoea excluded. Nutritional status: malnutrition excluded Hydration status: no participants were severely dehydrated Source of funding: Dexa Medica (Jakarta, Indonesia) provided the probiotics, and Indofarma (Jakarta, Indonesia) zinc and ORS, for free Median (range) duration of diarrhoea (hours) 68.5 (13 to 165) probiotic and 61.5 (21 to 166) control (P = 0.596). We did not convert these data to mean (SD) because IQR was not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization
Allocation concealment (selection bias)	Low risk	Sequential, identical envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias)	Low risk	Follow-up ≥ 90% in both groups

Hegar 2015 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Low risk	Pre-stated outcome reported

Henker 2007a

Study characteristics	
Methods	Randomized controlled trial; 11 centres Duration: 3 months (February to April 2005)
Participants	Inclusion criteria: outpatients; infants and toddlers < 4 years with > 3 watery or loose and non-bloody stools/d for ≤ 3 days Exclusion criteria: > 5% dehydration; intake of *E coli* Nissle 1917 in last 3 months; intake of food supplements or drugs that contain living micro-organisms or their metabolic products or components within 7 days before enrolment or during the trial; other anti-diarrhoeal drugs; breast-feeding, premature birth; severe or chronic disease of the bowel or severe concomitant disease. Antibiotics stated as exclusion criteria but some children included Numbers completing the study: 54/55 (98.2%) probiotic and 45/58 (77.6%) control. Reasons for withdrawal in both groups stated as intervention no longer suitable or required other treatment. All randomized participants included in analyses
Interventions	• Live *E coli* strain Nissle 1917 (Mutaflor suspension; 100 to 300 × 10^6 organisms/d according to age) • Placebo
Outcomes	• Number of stools, stool consistency, admixture of blood or mucus • Frequency of vomiting, abdominal pain, and cramps • Fluid intake, concomitant medication, and general state of health for up to 10 days Diarrhoea resolution: reduction in stool frequency to < 3 watery or loose stools in 24 hours over a period of at least 2 consecutive days Adverse effects: in the probiotic group, 1 had rhinitis and 1 had abdominal cramps. In the placebo group, 2 had acute otitis media and 1 showed poor compliance. No adverse events attributed to probiotic
Notes	Study location: Ukraine, Russia (low child, high adult mortality) Cause of diarrhoea: bloody diarrhoea excluded; 16/55 (29.1%) probiotic and 19/58 (32.8%) control had viral diarrhoea. Bacterial pathogens isolated from 9/55 (16.4%) probiotic and 4/58 (6.8%) control Nutritional status: most children well nourished Hydration status: > 5% dehydration excluded; 0/55 probiotic and 1/58 control children had mild dehydration Better outcomes with probiotic than placebo for abdominal pain (28/30 vs 24/33) and abdominal cramps (17/18 vs 21/26) Parents reported slightly better tolerance of probiotic than placebo, although investigators noted no difference Study authors supplied data regarding SDs for diarrhoea duration Source of funding: ARDEYPHARM provided verum and placebo medications and reimbursed study-related expenses

Henker 2007a *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomly permuted blocks of 4
Allocation concealment (selection bias)	Unclear risk	Unclear method of allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Study personnel blinded to intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcomes reported for > 90% in both groups
Selective reporting (reporting bias)	Low risk	Pre-stated outcome reported

Henker 2008

Study characteristics	
Methods	Randomized controlled trial; 11 centres Duration: 3 months (February to April 2005)
Participants	Inclusion criteria: inpatients; > 3 loose or watery stools without blood/24 hours for > 4 days and < 14 days; moderate dehydration (5% to 10% loss of body weight) Exclusion criteria: other severe organic or infectious disease; participation in another trial; intake of trial preparation in the past 3 months; intake of probiotic preparation within the past 7 days; antibiotic or anti-diarrhoeal; severe dehydration (> 10% weight loss); weight < 5th percentile; growth faltering; breast-feeding; preterm birth Numbers completing study: 72/75 (96.0%) probiotic (trial intervention no longer suitable/different treatment needed 2; personal reasons 1); 59/76 (77.6%) control (trial intervention no longer suitable/different treatment needed 11; personal reasons 5; intolerable adverse event 1). All randomized participants included in analyses
Interventions	• *Escherichia coli* strain Nissle 1917 (Mutaflor Suspension, Germany; participants received 100 to 300 × 10^6 organisms/d according to age) • Placebo - Identical suspension
Outcomes	• Resolution of diarrhoea (≤ 3 watery or loose stools/24 hours for 4 consecutive days) • Clinical improvement • General state of health • Adverse events • Tolerance of intervention

Henker 2008 *(Continued)*

	1 participant in probiotic group had a mild hypersensitivity reaction, which was assessed as possibly related to the intervention. In the control group, 1 participant had vomiting, 1 abdominal pain, and 1 dermatitis, and 1 withdrew because of influenza. Study authors commented that the probiotic was safe and well tolerated
Notes	Study location: Ukraine, Russia (low child, high adult mortality) Cause of diarrhoea: bloody diarrhoea excluded; 12 (16.0) probiotic and 15 (21.1) control had viral diarrhoea. Bacterial pathogens isolated from 15 (20.0) probiotic and 19 (25.0) control Nutritional status: weight < 5th percentile and growth faltering excluded; 2 (2.7) probiotic and 3 (3.9) control had mild/moderate malnutrition Hydration status: all had moderate dehydration (5% to 10% loss of body weight) Fewer children with dehydration at the end of the study in the probiotic group than in the placebo group. General state of health improved to a greater extent in the probiotic group than in the placebo group Significantly fewer children with diarrhoea > 21 days in the probiotic group than in the placebo group At the end of the study, the rates of mucus in stool, abdominal cramps, and abdominal pain were all lower in the probiotic group Source of funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomly permuted blocks of 4
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessed by parents; blinded to intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcomes reported for > 90% in both groups
Selective reporting (reporting bias)	Low risk	Pre-stated outcome reported

Hernandez 1998

Study characteristics

Methods	Randomized controlled trial; 1 centre

Hernandez 1998 *(Continued)*

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

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not adequately described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not adequately described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up ≥ 90% in both groups
Selective reporting (reporting bias)	High risk	No outcomes pre-stated

Hochter 1990

Study characteristics

Methods	Randomized controlled trial; multi-centre

Hochter 1990 *(Continued)*

	Duration: not stated
Participants	Inclusion criteria: outpatients, attending general practitioners, gastroenterologists, and internal physicians; adults with acute diarrhoea (> 3 liquid stools in last 24 hours; in great majority, duration 2 days or less; 1 participant in the placebo group had diarrhoea for > 10 days) Exclusion criteria: chronic diarrhoea; blood in stools; drug-induced diarrhoea; antimicrobial treatment; inflammatory bowel disease Numbers completing the study: 92/107 (86.0%) randomized participants completed the study (15 ineligible: 1 took additional drugs, 14 < 3 liquid stools at presentation). 3/92 participants dropped out (2 probiotic, 1 placebo) because intervention was not effective; results included in analysis
Interventions	• *S boulardii* (perenterol; 600 mg/d for 2 days, then 300 mg/d on days 3 to 7) • Placebo Interventions started at presentation
Outcomes	• Mean stool frequency on days 1, 3, and 8 • Score derived from stool frequency and consistency Mean (SD) stool frequency on day 1: 7.6 (4.2) probiotic, 6.9 (3.3) placebo; day 3: 2.4 (2.1) probiotic, 3.0 (2.8) placebo (P = 0.019); day 8: 1.3 (1.1) probiotic, 1.6 (1.1) placebo No adverse events attributed to probiotic
Notes	Study location: Germany (very low child and adult mortality) Cause of diarrhoea: stool analyses in first 50 participants only: 2 had rotavirus and 3 *Salmonella* Nutritional status: all well nourished Hydration status: no data presented Source of funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcomes reported for > 90% in both groups

Hochter 1990 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Unclear if all outcomes reported

Hong Chau 2018

Study characteristics	
Methods	Randomized double-blind placebo-controlled trial; 1 centre Duration: 1 year (October 2014 to September 2015)
Participants	Inclusion criteria: children aged 9 to 60 months; hospitalized with acute watery diarrhoea; 3 watery stools/d without visible blood or mucus (duration not stated) Exclusion criteria: at least 1 episode of diarrhoea in the month before admission; known to have short bowel syndrome or chronic (inflammatory) gastrointestinal disease; immunocompromised or immunosuppressed; on prolonged steroid therapy; diagnosed as severely dehydrated Numbers completing study: 143/150 (95.3%) probiotics (3 withdrew; 1 was lost to follow-up; 3 were self-prescribed); 147/150 (98%) control (2 withdrew; 1 took only 6 doses of study medication)
Interventions	• *L acidophilus* LA-14 (Imexpharm Pharmaceutical Company (Cao Lanh, Vietnam)), 2 sachets of 1×10^8 CFUs twice daily for 5 days (not stated whether probiotic alive or killed) • Placebo: 2 sachets of identical tasting product containing maltodextrin excipient only (Imexpharm Pharmaceutical Company (Cao Lanh, Vietnam)) twice daily for 5 days All participants received standard of care according to national guidelines, including ORS and zinc; typically participants were not given antimicrobials but were not excluded if they were
Outcomes	• Time from first dose of study medication to the start of the first 24-hour period without diarrhoea, hours, median (IQR): 35 (20 to 68) probiotic and 43 (15 to 66) placebo (P = 1.62) • Total duration of hospitalization, median (IQR): 79 hours (54 to 104 hours) probiotic and 78 hours (53 to 104 hours) placebo • Stool frequency in the first 3 days after enrolment • Treatment failure (i.e. no resolution of diarrhoea during 5-day treatment, severe symptoms for which treatment was stopped, requirement for additional anti-diarrhoeal treatment) • Daily rotavirus and norovirus viral loads in patients with PCR amplification-positive faecal samples • Dynamics of *L acidophilus* colonization over the course of study follow-up • Adverse events Additional exploratory outcomes • Recurrence of diarrhoea (defined as a new diarrhoea episode since the initial episode, as assessed at the day 14(+3) follow-up visit) • Vomiting frequency in the first 3 days after enrolment No adverse events attributed to probiotic
Notes	Study location: Vietnam (low child and adult mortality) Cause of diarrhoea: bloody diarrhoea excluded. Rotavirus detected in 64/150 (43%) probiotic and in 56/150 (37%) control; norovirus detected in 30/150 (20%) probiotic and in 38/150 (25%) control. Bacterial pathogens: *Campylobacter* in 11/150 (7%), *Shigella* in 17/150 (11%), and *Salmonella* in 14/150 (9%) in the probiotic group; *Campylobacter* in18/150 (12%), *Shigella* in 20/150 (13%), and *Salmonella* in 21/150 (14%) in the control group Nutritional status: not stated

Hong Chau 2018 *(Continued)*

	Hydration status: severe dehydration excluded Source of funding: this work was supported by The Wellcome Trust and the OAK Foundation. SB is funded by a Sir Henry Dale Fellowship from the Wellcome Trust and the Royal Society (100087/Z/12/Z) Median (IQR) duration of diarrhoea (hours) 35 (20 to 68) probiotic and 43 (15 to 66) control (P = 1.62). Median (IQR) duration of diarrhoea (hours) in children with rotavirus diarrhoea 45 (21 to 76) probiotic (n = 64) and 48 (18 to 66) control (n = 56). We did not convert these data to mean (SD) because of non-normal distribution

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization list using block randomization
Allocation concealment (selection bias)	Low risk	Sequentially numbered treatment packs prepared according to randomization list
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors blinded to intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up ≥ 90% in both groups
Selective reporting (reporting bias)	Low risk	All pre-stated outcomes reported; no additional outcomes reported

Huang 2014

Study characteristics

Methods	Open-label randomized controlled trial; 1 centre Duration: 21 months (February 2009 to October 2010)
Participants	Inclusion criteria: aged 3 months to 14 years; hospitalized due to mild to moderate dehydration; acute diarrhoea for < 72 hours Exclusion criteria: immunodeficiency; severe abdominal distension with risk of bowel perforation; severe infection or sepsis; history of gastrointestinal tract surgery; multiple pathogens identified on culture; probiotic or antibiotic used in the preceding week; *Campylobacter*-positive, adenovirus-positive, or multiple pathogen-positive patients Numbers completing the study: 82/82 (100%) probiotics; 77/77 (100%) control
Interventions	• BIO-THREE (TOA Pharmaceutical Co. Ltd., Tokyo, Japan): *Bacillus mesentericus*, *Clostridium butyricum*, and *Enterococcus faecalis*; participants aged 6 years or younger: 1 tablet (3.48×10^8 CFUs of a mixture of *E faecalis* (3.17×10^8 CFUs), *C butyricum* (2.0×10^7 CFUs), and *B mesentericus* (1.1×10^7 CFUs)) 3 times

Huang 2014 *(Continued)*

	daily; aged 6 to 12 years: 2 tablets 3 times daily; aged 12 years or older: 3 tablets 3 times daily for 7 days (not stated whether probiotics alive or killed) Intervention was started after randomization. All participants received supportive treatment (IV fluid, ORS, rice, and half-strength milk formula)
Outcomes	• Severity of gastroenteritis (i.e. Vesikari score) • Presence of diarrhoea after 7 days of probiotic treatment • Average length of hospital stay • Stool frequency after admission No adverse events attributed to probiotic
Notes	Study location: Taiwan (low child and adult mortality) Cause of diarrhoea: rotavirus detected in 22/82 (26.8%) probiotic and in 20/77 (26%) control; *Salmonella* detected in 23/82 (28%) probiotic and in 25/77 (32.5%) control; unknown origin in 37/82 (45.1%) probiotic and in 32/77 (41.6%) control. Adenovirus, *Campylobacter*, and multiple-pathogen-positive patients excluded Nutritional status: not stated Hydration status: no participants had severe dehydration Source of funding: supported by a Kaohsiung Veterans General Hospital research project grant (No. VGHKS98-081) Secondary outcome reporting: adverse events not pre-specified in the methods but reported in the results

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated 2-block randomization list
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up ≥ 90% in both groups
Selective reporting (reporting bias)	Low risk	Pre-stated outcome reported

Isolauri 1994

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

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear who assessed outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up ≥ 90% in both groups
Selective reporting (reporting bias)	High risk	Outcomes not pre-stated in methods

Jasinski 2002

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

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Alternate allocation
Allocation concealment (selection bias)	Unclear risk	Alternative allocation but unclear if concealed
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not adequately described

Jasinski 2002 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors blinded to intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up ≥ 90% in both groups
Selective reporting (reporting bias)	Low risk	Pre-stated outcomes reported

Javeed 2018

Study characteristics	
Methods	Randomized controlled open trial; 1 centre Duration: 6 months (January to June 2017)
Participants	Inclusion criteria: aged 6 months to 5 years; acute watery diarrhoea; hospitalized Exclusion criteria: not stated Number completing study: 157/157 (100%) in both probiotic and control groups
Interventions	• *Saccharomyces boulardii*, 250 mg twice daily for 5 days • No probiotic Participants given ORS on admission; IV fluids as needed; ciprofloxacin if bacterial diarrhoea
Outcomes	• Duration of diarrhoea • Diarrhoea lasting ≥ 48 hours • Diarrhoea lasting ≥ 14 days Adverse events not stated
Notes	Study location: Pakistan (high child and adult mortality) Cause of diarrhoea: acute watery diarrhoea, cause not specified Nutritional status: not stated Hydration status: not stated Source of funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not adequately described
Allocation concealment (selection bias)	Low risk	Opaque envelopes used

Javeed 2018 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up ≥ 90% in both groups
Selective reporting (reporting bias)	Low risk	Pre-stated outcomes reported

Khan 2017

Study characteristics	
Methods	Randomized controlled trial; 1 centre Duration: 6 months (April to October 2015)
Participants	Inclusion criteria: both genders; aged 6 months to 5 years; duration of illness less than 7 days; watery diarrhoea Exclusion criteria: chronic diarrhoea; blood in stool; using antibiotics or probiotics; in coma; shock; persistent vomiting Whether children with dehydration were included/excluded is unclear Numbers completing study: 48/48 (100%) in both probiotic and control groups
Interventions	• *Lactobacillus reuteri*, 5 drops (100 million CFUs) per day for 5 days • Placebo, for 5 days Interventions started on admission. Participants given standard management protocol for diarrhoea including ORT
Outcomes	• Resolution of diarrhoea (not defined) • Duration of illness ≤ 36 hours: 62.5% probiotic and 39.5% placebo (P = 0.041) Adverse events not stated
Notes	Study location: Pakistan (high child and adult mortality) Cause of diarrhoea: not stated Nutritional status: not stated Hydration status: not clear Source of funding: not stated

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Khan 2017 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Placebo not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up ≥ 90% in both groups
Selective reporting (reporting bias)	Low risk	Pre-specified outcomes reported

Kianifar 2009

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

Kianifar 2009 *(Continued)*

	Cause of diarrhoea: non-bloody, non-bacterial diarrhoea (not defined) Nutritional status: not stated Hydration status: all had moderate dehydration; severe dehydration excluded Source of funding: grant from the Vice Chancellery for Research, Mashad University of Medical Sciences

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random numbers table
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors blinded to intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	Overall follow-up ≥ 90%; no marked differences between arms
Selective reporting (reporting bias)	High risk	Outcomes not pre-stated

Kowalska-Duplaga 1999

Study characteristics

Methods	Randomized controlled trial; 1 centre Duration: not stated
Participants	Inclusion criteria: unclear whether inpatients or outpatients, or both; aged < 24 months with acute rotavirus diarrhoea (> 3 loose or watery stools/24 hours lasting < 48 hours before inclusion) Exclusion criteria: not stated Numbers completing study: 33/33 (100%) probiotic and 30/30 (100%) control
Interventions	• Live *Bifidobacterium ruminatum* (2×10^9 CFUs/d for 5 days) • Placebo Timing of administration not stated
Outcomes	• Duration of diarrhoea, hours (definition for recovery from diarrhoea not stated), mean: 62 probiotic, 57 placebo (P = 0.6) • Risk of diarrhoea lasting > 72 hours: RR 1.3 (95% CI 0.67 to 2.6)

Kowalska-Duplaga 1999 *(Continued)*

	No adverse events attributed to probiotic
Notes	Study location: Poland (low child and adult mortality) Cause of diarrhoea: all rotavirus diarrhoea Nutritional status: no data presented Hydration status: dehydration status similar in both groups; no other data presented Source of funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not adequately described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up ≥ 90% in both groups
Selective reporting (reporting bias)	Low risk	Pre-stated outcome reported

Kowalska-Duplaga 2004

Study characteristics

Methods	Randomized controlled trial; 3 centres Duration: not stated
Participants	Inclusion criteria: inpatients; infants and children with 3 or more loose stools within 24-hour period of < 72 hours' duration Exclusion criteria: history of acute diarrhoea within 14 days preceding inclusion in the study; antibiotic treatment; received probiotic up to 7 days before participation in the study; exclusively breast-fed; chronic alimentary disease; diagnosis of malabsorption; lack of parental consent; lack of diarrhoea Numbers completing study: 86/87 (98.9%) probiotic and 87/89 (97.8%) placebo
Interventions	• *L acidophilus, B bifidum, L bulgaricus* (3.2×10^9 CFUs/d for 5 days) • Identical placebo (no details given)

Kowalska-Duplaga 2004 *(Continued)*

	Interventions administered from recruitment
Outcomes	• Duration of diarrhoea (defined as time to last loose stool) • Duration of diarrhoea in rotavirus-positive children • Diarrhoea severity • Vomiting • Weight gain • Duration of hospital stay Mean duration of diarrhoea reported for children with rotavirus diarrhoea No adverse effects attributed to probiotic
Notes	Study location: Poland (low child and adult mortality) Cause of diarrhoea: rotavirus identified in 31 (37.3%) probiotic and 22 (26.8%) placebo. Bacterial pathogens identified in 6 (7.2%) probiotic and 14 (17%) placebo Nutritional status: no data presented Hydration status: no data presented Source of funding: interventions provided by Allergon, Sweden

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Allocated according to order of presentation
Allocation concealment (selection bias)	High risk	Allocated according to order of presentation
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not adequately described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up ≥ 90% in both groups
Selective reporting (reporting bias)	Unclear risk	Unclear

Kurugol 2005

Study characteristics

Methods	Randomized controlled trial; 1 centre Duration: not stated

Kurugol 2005 *(Continued)*

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

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias)	High risk	Follow-up < 90% in both groups

Kurugol 2005 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Low risk	Pre-stated outcome reported

Lee 2001

Study characteristics

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

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo

Lee 2001 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up ≥ 90% in both groups
Selective reporting (reporting bias)	Low risk	Pre-stated outcome reported

Maity 2019

Study characteristics	
Methods	Randomized, double-blind, placebo-controlled clinical trial; 1 centre Duration: 3 months (January to March 2018)
Participants	Inclusion criteria: male and female; 18 to 65 years of age; symptoms of acute diarrhoea manifesting within 48 hours before entering the trial; ≥ 3 incidences of unformed stool and last stool passed of unformed consistency (type 7 Bristol stool form scale) within 24 hours before entering the trial; complaints of abdominal discomfort within the last hour; written informed consent by study participants Exclusion criteria: severe form of diarrhoea or symptoms of more severe disease complexity; purulent or bloody stools; presence of erythrocytes or leukocytes in stools; required antibiotic treatment; presence of ulcers Numbers completing study: 30/30 (100%) in both probiotic and control groups
Interventions	• *Bacillus coagulans* strain LBSC (DSM17654) (Advanced Enzyme Technologies Ltd., Thane, India) 3 times per day for 7 days • Placebo (maltodextrin 1 g) 3 times per day for 7 days Participants given supportive treatment as needed
Outcomes	• Time to last unformed stool • Number of unformed stools produced • Change in severity of abdominal pain • Time to complete resolution of abdominal discomfort • Complete remission of diarrhoea • Rate of reoccurrence • Quality of life (QoL) assessment • Adverse events or serious adverse events No adverse events attributed to probiotic
Notes	Study location: India (high child and adult mortality) Cause of diarrhoea: not specified Nutritional status: not stated Hydration status: not stated Source of funding: Advanced Enzyme Technologies Ltd provided technical inputs, study drugs, and laboratory facilities to carry out the study

Maity 2019 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Identical placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up ≥ 90% in both groups
Selective reporting (reporting bias)	Low risk	Pre-specified outcomes reported

Mao 2008

Study characteristics	
Methods	Randomized controlled trial; 1 centre Duration: not stated
Participants	Inclusion criteria: inpatients; infants and children with severe acute diarrhoea (defined as 1 watery or mucous stool or 3 or more loose stools daily for > 24 hours) Exclusion criteria: moderate or severe malnutrition; total or partial breast-feeding; diarrhoea > 48 hours; need for antibiotic treatment; allergy to cow's milk; gastrointestinal or other chronic pathology 12/212 (5.7%; 3 study groups) withdrawn after recruitment as they did not match the age criteria. Numbers completing study: 70/70 (100%) probiotic and 71/71 (100%) control
Interventions	• Live *B lactis* Bb12 (10^9 CFUs/g milk powder) and *S thermophilus* TH4 (5×10^8 CFUs/g milk powder) administered until 24 hours after diarrhoea ended • Same probiotic preparation at a lower dose; not included in this review • Milk-based, lactose-free formula Interventions administered after oral or parenteral rehydration
Outcomes	• Stool frequency and consistency daily until day 7 • Diarrhoea duration (end of episodes defined as first formed stool if followed by 2 consecutive non-watery stools or 12 hours without evacuation) • Failure of treatment No specific comment regarding adverse effects

Mao 2008 *(Continued)*

Notes	Study location: China; low child and adult mortality Cause of diarrhoea: rotavirus diarrhoea occurred in 87% and bacterial diarrhoea in 13% in both groups Nutritional status: moderate or severe malnutrition excluded Hydration status: no data presented Source of funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up ≥ 90% in both groups
Selective reporting (reporting bias)	Low risk	Pre-stated outcome reported

Narayanappa 2008

Study characteristics

Methods	Randomized controlled trial; 1 centre Duration: not stated
Participants	Inclusion criteria: inpatients; infants and children with acute rotavirus diarrhoea (stool frequency and consistency not stated) of duration ≤ 3 days Exclusion criteria: infectious diarrhoea other than rotaviral diarrhoea; serum sodium > 155 mmol/L or < 130 mmol/L; history of malabsorption, respiratory or systemic infection Numbers completing study: 40/40 (100%) probiotic and 40/40 (100%) control
Interventions	• Bifilac (species of bacteria not mentioned; information from manufacturers; *Streptococcus faecalis* T-110 30 million bacteria, *Clostridium butyricum* TO-A 2 million bacteria, *Bacillus mesentericus* TO-A 1 million bacteria, *Lactobacillus sporogenes* 50 million bacteria. Total of 249×10^6 bacteria/d for < 14 days) • Placebo (no details given)

Narayanappa 2008 *(Continued)*

	When interventions started is not stated
Outcomes	• Frequency of diarrhoea • Duration of diarrhoea • Amount of IV fluid given • Amount of ORF given • Rotavirus shedding No adverse effects attributed to the probiotic
Notes	Study location: India; high child and adult mortality Cause of diarrhoea: all rotavirus diarrhoea Nutritional status: no data presented Hydration status: no data presented Source of funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up ≥ 90% in both groups
Selective reporting (reporting bias)	Low risk	Pre-stated outcomes reported

Nixon 2012

Study characteristics

Methods	Double-blind randomized placebo-controlled trial; 1 centre Duration: 9 months (November 2008 to July 2009)
Participants	Inclusion criteria: aged 6 months to 6 years; presenting with a complaint of acute diarrhoea; English or Spanish speaking; had access to a telephone and was available to receive calls daily for 5 days

Nixon 2012 *(Continued)*

	Exclusion criteria: admitted to inpatient service; had risk factors for non-viral diarrhoea (prolonged diarrhoea longer than 7 days, gross blood, antibiotic exposure, or inflammatory bowel disease); immune compromised; risk factors for probiotic-associated systemic illness (indwelling central line, short gut syndrome); allergy to milk products Numbers completing study: 67/77 (87%) probiotics (10 lost to follow-up); 71/78 (91%) control (7 lost to follow-up)
Interventions	• *Lactobacillus casei*strain GG (Amerifit Brands, Cromwell, CT, USA), 1 capsule 2 times per day for 5 days (not stated whether probiotic alive or killed) • Placebo capsule containing inulin (Amerifit Brands), 2 times per day for 5 days Intervention started in paediatric emergency department. Participants advised to avoid yogurt
Outcomes	• Time to return of normal stool • Proportion returning to normal stool • Number of diarrhoeal stools • Overall ability of patients or parents to return to their normal activities • Return to medical care • Need for hospitalization No adverse events attributed to probiotic
Notes	Study location: USA (very low child and adult mortality) Cause of diarrhoea: bloody diarrhoea excluded Nutritional status: not stated Hydration status: not stated Source of funding: this study was sponsored by Amerifit Brands (Cromwell, CT, USA), which provided LGG and placebo powder, as well as a small monetary compensation for participants' telephone airtime; supported in part by CTSA Grants UL1 RR025750, KL2 RR025749, and TL1 RR025748 from the National Center for Research Resources (NCRR), a component of the NIH, and an NIH roadmap for Medical Research Median (IQR) duration of diarrhoea (hours) 60 (37, 111) probiotic and 74 (43, 120) control (P = 0.37). We did not convert these data to mean (SD) because of non-normal distribution. However, study authors provided the following further information regarding the duration of diarrhoea, which we have included in this review • Probiotic arm: N = 63; mean (SD) 2.8193 (1.49981) days • Placebo arm: N = 66; mean (SD) 3.0846 (1.64460) days

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random numbers table
Allocation concealment (selection bias)	Unclear risk	Staff doing allocation may have known identity of A and B
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical placebo

Nixon 2012 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors blinded to intervention until analyses completed
Incomplete outcome data (attrition bias) All outcomes	High risk	Overall follow-up <90%
Selective reporting (reporting bias)	Low risk	Pre-stated outcomes reported

Ozkan 2007

Study characteristics	
Methods	Randomized controlled trial; 1 centre Duration: 6 months (October 2004 to March 2005)
Participants	Inclusion criteria: inpatients and outpatients; previously healthy children; aged 6 months to 10 years; acute diarrhoea (not defined) Exclusion criteria: severe systemic infection or sepsis; chronic disease; previous antibiotics; anti-diarrhoeal drugs; primary/secondary immune deficiency Numbers completing study: 16/16 (100%) probiotic and 11/11 (100%) control
Interventions	• *S boulardii* (500 mg/d in 5 mL of water for 7 days) • Placebo Start of intervention unclear
Outcomes	• Number, characteristics, and frequency of stools • Blood tests (blood count and lymphocyte subsets, C-reactive protein, blood smear, complement, immunoglobulins, and cytokines) Mean (SD) number of stools on day 3: 1.68 (0.23) probiotic, 3.36 (0.38) placebo ($P < 0.05$); day 4: 0.43 (0.22) probiotic, 1.81 (0.42) placebo ($P < 0.05$); no significant differences between groups for stool frequency on days 1 and 2 No adverse events attributed to probiotic
Notes	Study location: Turkey (low child, low adult mortality) Cause of diarrhoea: 1 (6.3%) child in probiotic group and 0 in control group had bacterial diarrhoea Nutritional status: mild/moderate malnutrition in 2 (12.5%) probiotic and in 1 (9.1%) control Hydration status: severe dehydration in 1 (6.3%) in probiotic group and in 0 in control group; mild/moderate dehydration in 3 (18.8%) probiotic and 2 (18.2%) control Source of funding: Sanofi-Aventis (Paris, France) provided laboratory reagents and a commercial preparation of *S boulardii*

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Ozkan 2007 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear who assessed outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up ≥ 90% in both groups
Selective reporting (reporting bias)	Low risk	All outcomes reported

Pant 1996

Study characteristics	
Methods	Randomized controlled trial; 1 centre Duration: 6 weeks (July to mid-August 1993)
Participants	Inclusion criteria: inpatients; infants and children with > 3 watery stools in last 24 hours and diarrhoea for < 14 days Mean (SD) weight-for-age z score -1.15 (0.95) probiotic and -1.8 (1.4) placebo Exclusion criteria: exclusive breast-feeding; septicaemia Numbers completing study: 20/20 (100%) probiotic and 19/19 (100%) placebo. However, data extractable for subset with watery diarrhoea only: 14/20 (70%) probiotic and 12/19 (63.2%) placebo. No data for children with bloody stools presented
Interventions	• Live *Lactobacillus* GG (10^9 to 10^{10} CFUs bd for 2 days) • Placebo Interventions started after 6 hours ORF
Outcomes	• Mean duration of diarrhoea (time to last watery stool) • Mean stool frequency on days 1 and 2 Vomiting occurred in 1 child in the placebo group. No adverse events were attributed to probiotic
Notes	Study location: Thailand (low child and adult mortality) Cause of diarrhoea: bloody stools in 6 children in probiotic group and in 7 in placebo group. All negative for parasites and cryptosporidium; 2 rotavirus and 1 astrovirus patients in the probiotic group and 5 rotavirus patients in the control group Nutritional status: no data presented

Pant 1996 *(Continued)*

	Hydration status: severe dehydration in 2 (10%) probiotic and 4 (21%) control; mild/moderate dehydration in all remaining children Source of funding: Scientific Hospital Supplies, UK, provided the probiotic

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors blinded to intervention; code broken after analysis completion
Incomplete outcome data (attrition bias) All outcomes	High risk	Follow-up < 90%
Selective reporting (reporting bias)	Low risk	Pre-stated outcome reported

Park 2017

Study characteristics

Methods	Double-blind randomized placebo-controlled trial; 1 centre Duration: not stated
Participants	Inclusion criteria: aged 9 to 16 months; diagnosed as infected with rotavirus via a latex agglutination test Exclusion criteria: not stated Numbers completing study: 28/28 (100%) probiotics; 29/29 (100%) control
Interventions	• Lyophilized *Bifidobacterium longum* BORI and *Lactobacillus acidophilus* AD031 (BIFIDO Co., Ltd., Hongchun, Korea) packet (containing 20 billion CFUs/g of *B longum* BORI and 2 billion CFUs/g of *L acidophilus* AD031), twice a day within 10 minutes of each meal for 3 days • Placebo: visually identical packet containing probiotic-free skim milk powder (BIFIDO Co., Ltd., Hongchun, Korea), twice a day within 10 minutes of each meal for 3 days Timing of start of administration not stated
Outcomes	• Duration of fever • Frequency of diarrhoea • Frequency of vomiting

Park 2017 *(Continued)*

	• Duration of diarrhoea before and after the study period in both groups No adverse events attributed to probiotic
Notes	Study location: South Korea (low child and adult mortality) Cause of diarrhoea: all rotavirus diarrhoea Nutritional status: not stated Hydration status: not stated Source of funding: support of the “Cooperative Research Program for Agriculture Science & Technology Development (Project No. PJ01123001)”, the Rural Development Administration, and “the Promoting Regional specialized Industry (Project No. R0004140)”; the Ministry of Trade, Industry and Energy (MOTIE); and the Korea Institute for Advancement of Technology (KIAT), Republic of Korea

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"...double-blind, randomized, and placebo-controlled clinical study..."; no further description
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not adequately described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up ≥ 90% in both groups
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes reported; no additional outcomes reported

Phavichitr 2013

Study characteristics

Methods	Randomized double-blind placebo-controlled trial; 1 centre Duration: 18 months (April 2010 to September 2011)
Participants	Inclusion criteria: children aged 3 to 72 months; hospitalized due to acute diarrhoea; parents consented to participate Exclusion criteria: previously treated during this diarrhoeal episode with probiotics or another anti-diarrhoeal drug (i.e. kaolin, pectin, smectite, activated charcoal, racecadotril, or cholestyramine); had other gastrointestinal disease, chronic disease, or severe dehydration

Phavichitr 2013 *(Continued)*

	Numbers completing study: 53/53 (100%) probiotics; 53/53 (100%) control
Interventions	• Lyophilized combination of *Lactobacillus acidophilus* and *Bifidobacterium bifidum* (Infloran®) (Laboratorio Farmaceutico SIT); aged < 1 year: 1 capsule (containing a minimum of 1 billion organisms of *L acidophilus* and *B bifidum*, with lactose and magnesium stearate as excipients) twice daily; aged ≥ 1 year: 1 capsule 3 times daily for 7 days maximum or until cessation of diarrhoea • Placebo containing lactose and magnesium stearate excipients (Laboratorio Farmaceutico SIT); aged < 1 year: 1 capsule twice daily; aged ≥ 1 year: 1 capsule 3 times daily for 7 days maximum or until cessation of diarrhoea Intervention started after randomization. All participants given rehydration therapy (orally and intravenously)
Outcomes	• Direct medical costs (hospital and service expenses, drug cost in Thai Baht (THB)) • Total cost (direct medical cost and indirect cost, i.e. estimated parental income loss) • Length of stay (days), median (IQR): 2 (2 to 3) in probiotic group and 3 (2 to 4) in placebo group (P = 0.049) • Duration of illness (days), median (IQR): 4 (3 to 6) in probiotic group and 5 (4 to 6) in placebo group (P = 0.068) • Drug acceptability First day of hospitalization was counted as 1 day only if the patient was admitted before 4:00 PM; discharge day was counted as 1 day only if the patient left after 12:00 PM. Patients were discharged after recovery No serious adverse events attributed to probiotic; no comment regarding non-serious events
Notes	Study location: Thailand (low child and adult mortality) Cause of diarrhoea: rotavirus detected in 39.6% in the probiotic group and in 29.4 in the control group; bacteria detected in 8.2% probiotic and in 22.4% control. Bloody diarrhoea or mucus in 9.4% probiotic and in 13.2% control Nutritional status: not stated Hydration status: severe dehydration excluded Source of funding: probiotics and placebo and partial financial support for this study were provided by Laboratorio Farmaceutico SIT Median (IQR) duration of diarrhoea (days): 4 (3 to 6) probiotic and 5 (4 to 6) control (P = 0.068). We did not convert these data to mean (SD) because of non-normal distribution Median (IQR) duration of hospitalization (days): 2 (2 to 3) probiotic and 3 (2 to 4) control (P = 0.049); no decimal place reported; therefore calculation of standard deviation unreliable

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization
Allocation concealment (selection bias)	Unclear risk	No specific details of allocation concealment; not stated that envelopes were opaque
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical placebo

Phavichitr 2013 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not adequately described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up ≥ 90% in both groups
Selective reporting (reporting bias)	Low risk	Pre-stated outcomes reported

Rafeey 2008a

Study characteristics	
Methods	Randomized controlled trial; 1 centre Duration: 12 months (May 2005 to May 2006)
Participants	Inclusion criteria: inpatients; infants and children with 3 or more watery stools/d for less than 48 hours and clinical dehydration Exclusion criteria: bloody stools; hypovolaemic shock; acute systemic illness; antibiotic or anti-diarrhoeal medication 18/178 children were withdrawn mainly because of parent non-compliance; likely to have been withdrawn before recruitment. Numbers completing study: 40/40 (100%) probiotic and 40/40 (100%) placebo
Interventions	Children randomized to 1 of 4 groups: A, yogurt fermented with *L acidophilus;* B, *L acidophilus* supplement; C, conventional yogurt; D, placebo. Groups B and D selected for review • *L acidophilus (*10×10^9 CFUs/; duration of treatment not stated; unclear if live or killed) • Placebo (no details given) Start of administration not stated
Outcomes	• Weight change • Duration of hospital stay • Stool frequency on days 1, 2, and 3 • Signs and symptoms on day 3 Mean (SD) stool frequency on day 2: 4.0 (3.2) probiotic, 4.0 (3.6) placebo; on day 3: 1.4 (2.6) probiotic, 2.3 (2.6) placebo No adverse effects attributed to probiotic
Notes	Study location: Iran; low child and adult mortality Cause of diarrhoea: bloody diarrhoea excluded; no bacteria or parasites identified in stool samples Nutritional status: severe malnutrition excluded Hydration status: severe dehydration in 1/40 (2.5%) probiotic and 2/40 (5%) control; all the rest had mild/moderate dehydration Source of funding: supported by a grant from Tabriz Medical University

Rafeey 2008a *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Restricted randomization using random permuted blocks
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Different forms of treatment given
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear who assessed outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up ≥ 90% in both groups
Selective reporting (reporting bias)	Unclear risk	Primary outcomes not reported

Raza 1995

Study characteristics	
Methods	Randomized controlled trial; 1 centre Duration: 2 months (July and August 1993)
Participants	Inclusion criteria: inpatients; undernourished infants and children with > 3 watery stools in last 24 hours for < 14 days' duration and at least moderate dehydration Exclusion criteria: severe malnutrition; septicaemia Numbers completing study: 36/40 participants; 4 withdrawals (2 diagnosed with cholera, 1 developed pneumonia, 1 refused anything by mouth). Results presented for 19/21 (90.5%) in the probiotic group and for 17/19 (89.5%) in the placebo group
Interventions	• Live *Lactobacillus* GG ($2 \times 10^{11-12}$ CFUs/d for 2 days) • Placebo Interventions started after 4 to 6 hours ORF
Outcomes	• Stool frequency on days 1 and 2 • Frequency of vomiting on days 1 and 2 • Weight gain Outcomes for watery (non-bloody) diarrhoea also presented: mean (SD) stool frequency day 2 for probiotic (n = 16) vs placebo (n = 16) was 4.4 (2.0) vs 6.6 (4.2) (P ≤ 0.05), and persistent diarrhoea at 48 hours was seen in 5 (31%) vs 12 (75%) participants (P ≤ 0.01). Definition of persistent diarrhoea not stated

Raza 1995 *(Continued)*

	Less vomiting in the probiotic group; myoclonic jerks occurred in 1 child in each group. No adverse events were attributed to probiotic
Notes	Study location: Pakistan (high child and adult mortality) Cause of diarrhoea: bloody diarrhoea included Nutritional status: all had mild/moderate malnutrition; severe malnutrition excluded Hydration status: severe dehydration in 14 (66.7) probiotic and 7 (37) control; all the rest had moderate dehydration Duration of diarrhoea not measured (many children discharged before stool character had changed) Source of funding: Scientific Hospital Supplies, UK, provided the probiotic

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Allocation code broken after analysis completion
Incomplete outcome data (attrition bias) All outcomes	Low risk	Overall follow-up ≥ 90%; no marked differences between arms
Selective reporting (reporting bias)	Low risk	Pre-stated outcome reported

Rerksuppaphol 2010

Study characteristics

Methods	Double-blind randomized controlled trial; 1 centre Duration: 10 months (January to October 2008)
Participants	Inclusion criteria: children aged 2 months to 7 years; admitted to paediatric unit of Srinakharinwirot University Hospital with a diagnosis of diarrhoea (watery/mucous stool ≥ 3 times in 24 hours) of > 72 hours' duration Exclusion criteria: evidence of systemic infection; neurological disturbance; history of convulsions; conditions such as chronic immunodeficient gastrointestinal condition; severe dehydration; children who had received treatment with probiotics and medications that interfere with intestinal motility during the present illness

Rerksuppaphol 2010 *(Continued)*

	Numbers completing study: 20/22 (91%) in the room temperature probiotic group (2 for parental concern), 23/23 (100%) in the refrigerated probiotic group; 21/22 (95.5%) in the control group (1 for parental concern). All randomized participants were analysed
Interventions	• Live refrigerated *Lactobacillus acidophilus* (minimum 10^9/capsule) and *Bifidobacterium bifidum* (minimum 10^9/capsule) (Infloran, Berna, Switzerland) (data extracted for analysis) • *Lactobacillus acidophilus* (minimum 10^9/capsule) and *Bifidobacterium bifidum* (minimum 10^9/capsule) (Infloran, Berna, Switzerland) stored at room temperature (probiotic viability not assessed) (data not extracted for analysis) • Refrigerated placebo (capsule of powdered ORS identical in colour and size) Timing of onset of administration not stated. All capsules opened and powder dissolved in milk or some other fluid and given as 1 capsule 3 times daily until the end of diarrhoea and up to maximum of 5 days
Outcomes	• Duration of diarrhoea • Number of abnormal watery or mucous stools passed • Duration of hospital stay • Requirement for rehydration fluid No adverse events attributed to probiotic
Notes	Study location: Thailand (low child and adult mortality) Cause of diarrhoea: rotavirus detected in 7 (30.4%) in the refrigerated probiotic group and 9 (40.9%) in the room temperature probiotic group and in 5 (22.7%) in the control group Nutritional status: not stated Hydration status: mild/no dehydration 15 (68.2%) in the room temperature probiotic group, 18 (78.3%) in the refrigerated probiotic group, and 17 (72.3%) in the control group; moderate dehydration 7 (31.8%) in the room temperature probiotic group, 5 (21.3%) in the refrigerated probiotic group, and 5 (22.7%) in the control group; severe dehydration excluded Source of funding: this study was supported by grants from the Faculty of Medicine, Srinakharinwirot University, Thailand Median (IQR) duration of diarrhoea (hours) 28 (32) in the probiotic arm and 51.5 (44) in the control arm. Median (IQR) duration of hospitalization (hours) 46 (42) in the probiotic arm and 64 (48) in the control arm (P > 0.05). We did not convert these data to mean (SD) because of non-normal distribution

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization
Allocation concealment (selection bias)	Unclear risk	Not adequately described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessor blinded to intervention

Rerksuppaphol 2010 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up ≥ 90% in both groups
Selective reporting (reporting bias)	Low risk	Pre-stated outcome reported

Riaz 2012

Study characteristics	
Methods	Randomized double-blind placebo-controlled trial; 1 centre Duration: 17 months (May 2008 to September 2009)
Participants	Inclusion criteria: children aged 3 to 59 months; acute onset of diarrhoea (of < 48 hours); admitted to DTTU (diarrhoea treatment and training unit) Exclusion criteria: clinical evidence of severe malnutrition; systemic infection; encephalopathy and/or convulsion; electrolyte imbalance; invasive diarrhoea; previous use of any probiotics Numbers completing study: 43/54 (79.6%) in the probiotics group (6 left the study; 5 treatment failure); 47/54 (87%) in the control group (3 left study; 4 treatment failure). All 108 patients included in analysis
Interventions	• *Saccharomyces boulardii* (Econorm, Dr Reddy's Laboratories) 250 mg, mixed with puffed rice powder, twice daily for 5 days or to end of illness (whichever was sooner) (not stated whether probiotic alive or killed) • Placebo, in an identical packet, mixed with puffed rice powder, twice daily for 5 days or to end of illness Intervention was started following receipt of informed consent. All participants were managed with ORS, zinc, and feeding as per guidelines of the IAP task force on diarrhoea
Outcomes	• Duration of post-intervention diarrhoea (time from enrolment to recovery) • Total ORS consumed • Number of stools passed • Weight gain • Total IVF needed No adverse events attributed to probiotic
Notes	Study location: India (high child and adult mortality) Cause of diarrhoea: rotavirus detected in 14/93 (15.1%) samples tested; *V cholerae* detected in 4 (7.4%) in both probiotic and control groups. Invasive diarrhoea excluded Nutritional status: moderate malnutrition 19 in the probiotic group and 23 in the control group. Mean weight for age 75.84% (± 13.13) in the probiotic group and 72.87% (± 11.22) in the control group; mean weight for height 83.39% (± 10.72) in the probiotic group and 82.31% (± 10.82) in the control group. Severe malnutrition excluded (weight for age below 60% or weight for length/height below 70%) Hydration status: no dehydration 22 in the probiotic group and 23 in the control group; some dehydration 26 in the probiotic group and 24 in the control group; severe dehydration 6 in the probiotic group and 7 in the control group Source of funding: no role for funding source in this trial
Risk of bias	

Riaz 2012 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	External block randomization
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not adequately described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcomes reported for > 90% in both groups
Selective reporting (reporting bias)	Low risk	Pre-stated outcome reported

Ritchie 2010

Study characteristics	
Methods	Randomized controlled trial; 1 centre Duration: 21 months (June 2002 to March 2004)
Participants	Inclusion criteria: inpatients; Aboriginal children aged 4 months to 2 years with acute diarrhoea defined as ≥ 3 loose stools during 24 hours before presentation and duration < 7 days; able to tolerate ORF Exclusion criteria: oxygen required during the study period; chronic cardiac, renal, or respiratory disease; previous gastrointestinal surgery; proven sucrose intolerance; suspected or known immunodeficiency; received probiotic before enrolment; younger than 4 months Numbers completing study: 201 assessed for eligibility; 103 refused participation and 28 failed to consent. Probiotic arm: 4 discharged before intervention, 1 parental withdrawal, 33/38 (86.8%) completed study. Control arm: 1 parental withdrawal, 31/32 (96.9%) completed study
Interventions	• Live *L casei* strain GG (> 15×10^9 CFUs/d for 3 days) • Identical placebo (no details given) Interventions administered within 24 hours of admission
Outcomes	• Small intestinal absorption capacity • Diarrhoea duration (defined as time to last loose stool in which fewer than 3 loose stools occurred within a 24-hour period) • Diarrhoeal frequency • Total stool output • Proportion of participants with diarrhoea on days 3 and 4 • Change in body weight on days 1 and 4 • Total ORF and IV fluid required

Ritchie 2010 *(Continued)*

	• Safety and tolerability No adverse events attributed to probiotic
Notes	Study location: Australia (very low child and low adult mortality). However, this study recruited Aboriginal children who commonly had comorbidities such as pneumonia and malnutrition related to poverty and social disadvantage in the top end of the Northern Territory. Therefore, data not included in analysis according to country mortality strata Cause of diarrhoea: bacterial pathogens identified in 4 (12%) probiotic and 4 (13%) control; rotavirus identified in 11 (33%) probiotic and 6 (19%) control; parasites identified in 2 (6%) probiotic and 2 (6%) control Nutritional status: mild/moderate malnutrition common amongst participants; no other data presented Hydration status: severe dehydration in 0 probiotic and in 1 (3.2%) control; all the rest had mild/moderate dehydration Source of funding: project supported by Australian National Health and Medical Research Council

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated block randomization
Allocation concealment (selection bias)	Unclear risk	No specific details of allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors blinded to intervention
Incomplete outcome data (attrition bias) All outcomes	High risk	Overall follow-up ≥ 90%, but marked differences (> 10%) between study arms
Selective reporting (reporting bias)	Low risk	Pre-stated outcomes reported

Rosenfeldt 2002a

Study characteristics

Methods	Randomized controlled trial; 2 centres Duration: 6 months (December 1998 to May 1999)
Participants	Inclusion: inpatients; children aged 6 to 36 months with 2 or more consecutive loose stools in 24 hours and duration no longer than 7 days

Rosenfeldt 2002a *(Continued)*

	Exclusion criteria: underlying chronic disease; antibiotics prescribed during the study period Numbers completing study: 86 children enrolled, of whom 69 (80.2%) completed the study; exclusions were made after randomization because antibiotics were prescribed (3 in the control group and 2 in the probiotic group); rapid recovery before intervention started (3 in the control group and one in the probiotic group); non-compliance with the protocol (4 in the control group and 4 in the probiotic group)
Interventions	• Live *L rhamnosus* 19070-2 and *L reuteri* DSM 12246 (2×10^9 CFUs of each organism/d for 5 days) • Identical placebo (skimmed milk powder and dextrose anhydrate) Interventions started as soon as possible after randomization and no wait for rehydration
Outcomes	• Duration of diarrhoea (time from treatment start to appearance of first normal stool as recorded by parents) • Persistence of diarrhoea at end of intervention (day 5) No adverse events attributed to probiotic
Notes	Study location: Denmark (very low child and adult mortality) Cause of diarrhoea: overall, rotavirus was the only pathogen in 40 (58%) children; 6 children had rotavirus and a bacterial pathogen was identified; in addition, *Campylobacter jejuni* was isolated in 3 children, and *Salmonella typhimurium* in 1 child Nutritional status: no data presented Hydration status: no severe dehydration; mild/moderate dehydration in 5 (16.7%) probiotic and in 17 (43.6%) control 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 in the control group (mean 1.6 (SD 1.0) vs 2.7 (SD 2.0), respectively; P = 0.02) Probiotics also appeared to reduce significantly the number of children excreting rotavirus in stools on day 5 Source of funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias)	High risk	Follow-up < 90% in both groups

Rosenfeldt 2002a *(Continued)*
All outcomes

Selective reporting (reporting bias)	Low risk	Pre-stated outcomes reported

Rosenfeldt 2002b

Study characteristics	
Methods	Randomized controlled trial; 19 day care centres Duration: 6 months (December 1998 to May 1999)
Participants	Inclusion criteria: outpatients; children aged 6 to 36 months with 2 or more consecutive loose stools in 24 hours as assessed by parents and with duration no longer than 7 days Exclusion criteria: underlying chronic disease; antibiotics prescribed during study period Numbers completing study: 50 children enrolled, of whom 43 (86%) participants completed the study. Exclusions were made because of hospitalization with excessive vomiting and moderate dehydration (2 in the placebo group and 3 in the probiotic group), prescribed antibiotics (1 in placebo group), and non-compliance with protocol (1 in placebo group)
Interventions	• Live *L rhamnosus* 19070-2 and *L reuteri* DSM 12246 (2×10^9 CFUs of each organism/d for 5 days) • Identical placebo Interventions started as soon as possible after randomization
Outcomes	• Duration of diarrhoea (time from treatment start to appearance of first normal stool as recorded by parents) • Persistence of diarrhoea at end of intervention (day 5) One participant in the probiotic group complained of constipation (no stools passed from day 3 for 10 days). No adverse events attributed to probiotic
Notes	Study location: Denmark (very low child and adult mortality) Cause of diarrhoea: overall, rotavirus was the only pathogen in 25 children, 2 had rotavirus and a bacterial pathogen identified, 2 had infection with *C jejuni* and *Salmonella typhimurium* Nutritional status: no data presented Hydration status: mild/moderate dehydration in 3 patients (12.5%) in the probiotic group and in 4 (13.8%) in the control group; no severe dehydration Probiotics appeared to reduce significantly the duration of diarrhoea in children treated within 60 hours of the onset of diarrhoea Source of funding: not stated

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described

Rosenfeldt 2002b *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not adequately described
Incomplete outcome data (attrition bias) All outcomes	High risk	Follow-up < 90% in both groups
Selective reporting (reporting bias)	Low risk	Pre-stated outcome reported

Sarkar 2005

Study characteristics	
Methods	Randomized controlled trial; 1 centre Duration: 23 months (February 2001 to December 2002)
Participants	Inclusion criteria: inpatients; boys aged 4 to 24 months; acute watery diarrhoea (> 4 liquid stools during 24 hours) of < 48 hours' duration Exclusion criteria: severe malnutrition (< 65% weight for age by the standard of the National Centre for Health Statistics (NCHS)); systemic infection requiring antimicrobial therapy; bloody diarrhoea; spot sample of stool revealed *V cholerae* by dark-field microscopy; antibiotic treatment in the preceding 2 weeks Numbers completing study: 112/115 (97.4%) probiotic (3 withdrawn by parents) and 115/115 (100.0%) control
Interventions	• Live *Lactobacillus paracasei* strain ST11 (10^{10} CFUs/d for 5 days) • Placebo (whey-protein and skimmed milk powder blend) Interventions started after enrolment. All children received ORF and continued feeding, including breast milk if breast-fed
Outcomes	• Stool output and frequency • Oral rehydration solution intake • Daily excretion of rotavirus No comment regarding adverse outcomes
Notes	Study location: Bangladesh (high child and adult mortality) Cause of diarrhoea: bloody diarrhoea excluded. Rotavirus detected in 78 (69.6%) in the probiotic group and in 73 (63.5%) in the placebo group; *V cholera* detected in 14 (12.2%) probiotic and in 16 (13.9%) placebo

Sarkar 2005 *(Continued)*

Nutritional status: severe malnutrition (weight < 65% weight for age of NCHS standard) excluded; no further data presented

Hydration status: mild/moderate dehydration in 54 (47.0%) probiotic and in 65 (56.5%) control

Source of funding: Nestlé Research provided *L paracasei.* Research supported by the Swedish Agency for Research in Developing Countries, the Karolinska Institute (Stockholm, Sweden), and Nestlé Research Centre (Lausanne, Switzerland)

Rotavirus outcomes: results presented for < 90% of patients

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly permutated blocks
Allocation concealment (selection bias)	Unclear risk	Unclear method of allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors blinded to allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Overall follow-up ≥ 90% for primary outcome
Selective reporting (reporting bias)	Low risk	Pre-stated outcome reported

Schnadower 2018

Study characteristics

Methods	Prospective double-blind randomized placebo-controlled trial; 10 centres Duration: 3 years (July 2014 to June 2017)
Participants	Inclusion criteria: age 3 months to 4 years; diagnosed with acute gastroenteritis by an ED provider Exclusion criteria: risk factors for bacteraemia; chronic gastrointestinal disorder; pancreatitis; bilious emesis; hematochaezia; allergy to *L rhamnosus* GG, microcrystalline cellulose, erythromycin, clindamycin, and beta-lactam antibiotic agents; caregiver did not speak English or Spanish Numbers completing study: 468/483 (96.9%) probiotic (15 lost to follow-up) and 475/488 (97.3%) control (13 lost to follow-up)
Interventions	• Live *Lactobacillus rhamnosus* GG (Chr Hansen), 1×10^{10} CFUs twice daily for 5 days • Placebo, twice daily for 5 days

Schnadower 2018 *(Continued)*

	Interventions started after randomization in the ED
Outcomes	• Modified Vesikari scale • Frequency and duration of diarrhoea • Frequency and duration of vomiting • Incidence of unscheduled healthcare visits for symptoms of gastroenteritis within 2 weeks after index visit • Number of days of day care missed by participants • Number of hours of work missed by caregivers • Rate of household transmission • Safety Adverse events reported in 63 (13.3%) and 62 (12.9%) in the probiotic and placebo groups, respectively; serious adverse events reported in 8 (1.7%) in the probiotic group and in 13 (2.7%) in the placebo group Study authors were contacted and provided data for the outcomes in this review, including for children with rotavirus diarrhoea
Notes	Study location: USA (very low child and adult mortality) Cause of diarrhoea: of those who had a stool sample tested (379 in the probiotic group and 382 in the placebo group), 75 (19.8%) and 60 (15.7%) had rotavirus A, 79 (20.8%) and 70 (18.3%) had norovirus GI/GII, 28 (7.4%) and 41 (10.7%) had adenovirus 40/41, 25 (6.6%) and 31 (8.1%) had *Clostridium difficile* toxin A/B, 23 (6.1%) and 15 (3.9%) had *Shigella,* and 153 (40.4%) and 173 (45.3%) had no pathogen detected in the probiotic and placebo groups, respectively Nutritional status: not stated Hydration status: 133/483 (27.5%) in the probiotic group and 133/488 (27.3%) in the placebo group had dehydration Source of funding: Eunice Kennedy Shriver National Institute of Child Health and Human Development and others. Product and placebo were provided in kind by iHealth, the distributors of Culturelle in the United States

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Web-based randomization (www.randomize.net)
Allocation concealment (selection bias)	Low risk	Web-based system
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical placebo; participants and personnel who assessed trial outcomes were unaware of trial group assignments
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants and personnel who assessed trial outcomes were unaware of trial group assignments
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up ≥ 90% in both groups

Schnadower 2018 *(Continued)*

Selective reporting (reporting bias)	Low risk	Pre-specified outcomes reported

Shornikova 1997a

Study characteristics	
Methods	Randomized controlled trial; 1 centre Duration: 1 year (1 April 1994 to 31 May 1995)
Participants	Inclusion criteria: inpatients; infants and children with ≥ 1 watery stool in the last 24 hours and diarrhoea for < 5 days Exclusion criteria: not stated Numbers completing study: 123/214 (57%) eligible children admitted during the study period enrolled; no reasons given for those not recruited. A total of 59/59 (100%) children allocated to the probiotic group and 64/64 (100%) in the placebo group completed the trial
Interventions	• Live *L* strain GG (American-type culture collection 53 103; 10^{10} CFUs/d as a dried powder for 5 days) • Placebo Interventions started with oral rehydration solution. All participants with positive stool cultures received antibiotics Effect of isotonic vs hypotonic oral rehydration solution also assessed
Outcomes	• Duration of diarrhoea (defined as last appearance of watery stools) • Weight gain • Duration of hospital stay No comment regarding adverse events
Notes	Study location: Russia (low child and high adult mortality) Cause of diarrhoea: rotavirus identified in 13 (22.0%) probiotic and in 21 (32.8%) control. Bacterial diarrhoea identified in 11 (18.7%) probiotic and in 15 (23.4%) control Nutritional status: no data presented Hydration status: mean dehydration ~ 4% in both groups Among children with rotavirus diarrhoea, the probiotic (n = 13) reduced the number of watery stools compared with placebo (n = 21; P = 0.02, but no data given). No beneficial effect of the probiotic was seen in those with bacterial diarrhoea (probiotic (n = 11) and placebo (n = 115); P = 0.42) Stool samples tested for rotavirus (Rotazyme, Dakopotts AS, Denmark) and cultured for *Salmonella* and *Shigella* Source of funding: Leiras, Turku, Finland, and Valio, Helsinki, Finland Secondary outcome reporting: duration of hospital stay not pre-specified in the methods but reported in the results

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Shornikova 1997a *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Not adequately described
Allocation concealment (selection bias)	Unclear risk	No specific details of allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not adequately described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not adequately described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow up ≥ 90% in both groups
Selective reporting (reporting bias)	Low risk	Pre-stated outcome reported

Shornikova 1997b

Study characteristics	
Methods	Randomized controlled trial; 2 centres Duration: 6 months (22 January to 15 July 1996)
Participants	Inclusion criteria: inpatients; infants and children with ≥ 3 watery stools in last 24 hours; diarrhoea for < 7 days; stools positive for rotavirus antigen (IDEIA rotavirus, UK). Mean dehydration about 4% in both groups Exclusion criteria: 20 participants who received exclusively or mainly IV fluids were excluded 86/97 (89%) enrolled participants were positive for rotavirus Numbers completing study: 97 patients enrolled; 86 were positive for rotavirus; 21 in the probiotics group and 25 in the placebo group (and 20 allocated to a low-dose probiotic group) did not require IV rehydration and were analysed
Interventions	Participants randomized to 1 of 3 groups: 20 in the probiotic small dose (10^7 CFUs/d) group, 21 in the probiotic large dose group, 25 in the placebo group. Data from the large dose group were used in this review • Live *L reuteri* (10^{10} to 10^{11} CFUs/d for maximum 5 days) • Live *L reuteri* (10^7 CFUs/d for maximum 5 days) • Placebo Interventions started with ORF
Outcomes	• Duration of diarrhoea (time to last watery stool in a 24-hour period with no watery stools) • Stool frequency on day 2 of treatment • Weight gain No comment regarding adverse events

Shornikova 1997b *(Continued)*

Notes	Study location: Finland (very low child and adult mortality) Cause of diarrhoea: all rotavirus Nutritional status: no data presented Hydration status: mean dehydration about 4% in both groups Data from high-dose probiotic group used for continuous outcomes Duration of diarrhoea before admission greater in probiotic group (4.2 (SD 1.4) days) than in placebo group (2.9 (SD 1.2) days). Number with persistent diarrhoea on day 3 derived from graph Source of funding: BioGaia Biologicals AB

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Different dosing schedules
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear who assessed outcomes
Incomplete outcome data (attrition bias) All outcomes	High risk	Follow-up < 90%
Selective reporting (reporting bias)	Low risk	Pre-stated outcomes reported

Shornikova 1997c

Study characteristics

Methods	Randomized controlled trial; 1 centre Duration: 5 months (29 January to 3 July 1995)
Participants	Inclusion criteria: inpatients; infants and children with ≥ 3 watery stools in last 24 hours; diarrhoea for < 7 days; ingested bovine dairy products Exclusion criteria: immunosuppressive therapy or immune deficiency; allergy to bovine milk; serious underlying disorder; receiving an investigational product during the preceding month Numbers completing study: 41 participants initially enrolled: 19/19 (100%) probiotic and 21/22 (95.5%) placebo (1 participant in the placebo group was removed because the probiotic agent (*L reuteri*) was detected in stool; the probiotic was administered to his sibling)

Shornikova 1997c *(Continued)*

Interventions	• Live *L reuteri* SD 2112 (10^{10} to 10^{11} CFUs/d for maximum of 5 days) • Placebo Interventions started at recruitment
Outcomes	• Weight gain • Duration of diarrhoea (last appearance of watery stools) • Number of participants with watery diarrhoea according to day of treatment • Stool frequency on days 2 and 3 • Number of participants with vomiting according to day of treatment Less vomiting in the probiotic group. No adverse events attributed to probiotic
Notes	Study location: Finland (very low child and adult mortality) Cause of diarrhoea: rotavirus identified in 18 (86%) probiotic and in 12 (63%) control Nutritional status: no data presented Hydration status: mean dehydration at baseline greater in the probiotic group (3.9% (SD 1.3)) than in the control group (3.0 (SD 1.2)) Source of funding: BioGaia Biologicals, Inc., Raleigh, NC, USA

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not adequately described
Allocation concealment (selection bias)	Unclear risk	Not adequately described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Matching placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear who assessed outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up ≥ 90% in both groups
Selective reporting (reporting bias)	Low risk	Pre-stated outcome reported

Simadibrata 2013

Study characteristics

Methods	Prospective double-blind randomized controlled trial; 3 centres

Simadibrata 2013 *(Continued)*

	Duration: 2007 to 2010
Participants	Inclusion criteria: acute diarrhea; aged 13 to 60 years; no severe complications Exclusion criteria: serious complication (renal failure, metabolic acidosis, severe dehydration, hypovolaemic shock, heart failure, vomiting, anorexia); history of allergy to *Lactobacillus* spp; diarrhoea caused by amoeba, colorectal cancer, or tumour; exclusion criteria with proven cause of diarrhoea, amoeba, colorectal cancer, or tumour; taking antibiotic therapy Numbers completing study: 38/45 (84.4%) probiotics (reason for withdrawals not stated); 38/45 (84.4%) control (reason for withdrawals not stated). All randomized patients analysed
Interventions	• *Lactobacillus rhamnosus* R0011 and *Lactobacillus acidophilus* R0052 (Lacidofil) (not stated whether probiotic alive or killed), 2 capsules (containing *L rhamnosus* (1.9×10^9 CFUs) and *L acidophilus* (0.1×10^9 CFUs)) 3 times daily for 7 days • Placebo: 2 capsules 3 times daily for 7 days Intervention started as soon after informed consent received as possible. All participants received ORS (Oralit®)
Outcomes	• Stool frequency • Stool consistency • Abdominal pain, nausea, vomiting, bloating, tenesmus, headache, fever, thirst No serious adverse events attributed to probiotic; no comment regarding non-serious events
Notes	Study location: Indonesia (low child and adult mortality) Cause of diarrhoea: pathogen (not defined) detected in 8/38 (21.1%) probiotic and in 7/38 (18.4%) control. Amoebic diarrhoea excluded Nutritional status: not stated Hydration status: severe dehydration excluded Source of funding: financially supported by Dexa Medica Ltd and Rossel Institute

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not adequately described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	High risk	Follow-up < 90% in both groups

Simadibrata 2013 *(Continued)*

Selective reporting (reporting bias)	Low risk	Pre-stated outcomes reported

Sirsat 2017

Study characteristics	
Methods	Randomized controlled trial; 1 centre Duration: not stated
Participants	Inclusion criteria: children aged 2 months to 5 years; presenting with acute watery diarrhoea Exclusion criteria: not stated Numbers completing study: 145/145 (100%) probiotic; 145/145 (100%) control
Interventions	• *Saccharomyces boulardii*, 50 mg/kg/d, diluted in water or mixed with semi-solid food; duration not stated Timing of onset of intervention not stated All participants received oral rehydration solution
Outcomes	• Stool consistency • Stool frequency • Duration of diarrhoea • Appearance of first semi-formed stool • Rotavirus antigen positive • Frequency of diarrhoea after 5 days in those with lactose intolerance • Percentage hospitalized for less than 3 days No comment regarding adverse events
Notes	Study location: India (high child and adult mortality) Cause of diarrhoea: rotavirus detected in 88/145 (60.7%) probiotic and in 77/145 (53.1%) control Nutritional status: not stated Hydration status: not stated Source of funding: none declared The frequency of diarrhoea after the third day of intervention was reduced in 60 (64%) probiotic vs 30 (39%) control (P < 0.001)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomization using random numbers table
Allocation concealment (selection bias)	Unclear risk	Not stated

Sirsat 2017 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No mention of who assessed outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up ≥ 90% in both groups
Selective reporting (reporting bias)	Low risk	All outcomes reported

Sudha 2019

Study characteristics	
Methods	Double-blind randomized placebo-controlled parallel-group study; 2 centres Duration: September to November 2017
Participants	Inclusion criteria: patients of either sex; aged 6 months to 5 years; clinical diagnosis of acute diarrhoea; not had any major illnesses; parents willing to give written informed consent and to follow study procedures Exclusion criteria: severe malnutrition; requiring antibiotics during study period; severe diarrhoea (requiring treatment other than investigational product and ORS); visible blood in stool; use of probiotics, antibiotics, or any anti-diarrhoeal medication in the last 3 weeks; participation in any clinical trial or usage of any investigational product in the past 90 days; hypersensitivity to any of the active substances or excipients; previous use (within 48 hours) of kaolin, pectin, bismuth subsalicylate, racecadotril, loperamide, atropine, and other anticholinergic agents Numbers completing study: 59/60 (98.3%) probiotic (withdrawal due to protocol violation); 60/60 (100%) control
Interventions	• *Bacillus clausii* UBBC-07 (not stated whether probiotic alive or killed) 2×10^9 spores/5 mL 2 times daily for 5 days • Placebo suspension (purified water) 2 times daily for 5 days Timing of start of administration not stated. All participants received ORS
Outcomes	• Decrease in frequency of diarrhoea • Decrease in duration of diarrhoea • Improvement in consistency of stool • Decrease in frequency and duration of vomiting episodes • Decrease in duration of fever
Notes	Study location: India (high child and adult mortality) Cause of diarrhoea: bloody diarrhoea excluded Nutritional status: severe malnutrition excluded

Sudha 2019 *(Continued)*

	Hydration status: not stated Source of funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated block randomization
Allocation concealment (selection bias)	Low risk	Opaque, sealed envelopes used
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unclear whether placebo identical
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Investigators blinded to treatment group
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up ≥ 90% in both groups
Selective reporting (reporting bias)	Low risk	All pre-defined outcomes reported

Szymanski 2006

Study characteristics

Methods	Randomized controlled trial; 1 centre Duration: 10 months (September 2003 to June 2004)
Participants	Inclusion criteria: inpatients and outpatients; aged 2 months to 6 years with acute diarrhoea (3 or more stools/d looser than normal that may contain blood or mucus for > 1 and < 5 days) Exclusion criteria: organic gut disease; underlying chronic illness; immunosuppression; exclusive breast-feeding Numbers completing study: 46/49 (93.9%) probiotic; 41/44 (93.2) control. Withdrawals stated to be due to non-compliance or incomplete data
Interventions	• 3 live strains of *L rhamnosus* 573L/1, 573L/2, 573L/3 (2.4×10^{10} CFUs/d; Lakcid L, Biomed, Lublin, Poland) given orally in glucose • Identical placebo Start of intervention delayed > 72 hours for many participants
Outcomes	• Duration of diarrhoea (either no abnormal movement for the last 12 hours or time to second normal stool) • Weight gain after rehydration • Number of stools/d

Szymanski 2006 *(Continued)*

	• Duration of IV fluids • Diarrhoea > 7 days • Gut colonization with probiotics No adverse events attributed to probiotic
Notes	Study location: Poland (low child and adult mortality) Cause of diarrhoea: bloody diarrhoea included. Overall, 39/87 (45%) had rotavirus (22 probiotic and 17 control), 5/87 (6%) had adenovirus, 9/87 (10%) had a bacterial pathogen, and many children had norovirus infection Nutritional status: no data presented Hydration status: no severe dehydration. Mild/moderate dehydration in 34 (73.9%) probiotic and in 31 (75.6%) control Source of funding: Wellcome Travel Award

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated block randomization
Allocation concealment (selection bias)	Unclear risk	Unclear method of allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Randomization code broken after study completion
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up ≥ 90% in both groups
Selective reporting (reporting bias)	Low risk	Pre-stated outcome reported

Szymanski 2019

Study characteristics

Methods	Randomized double-blind placebo-controlled trial; 1 centre Duration: January 2017 to November 2018
Participants	Inclusion criteria: younger than 5 years of age; acute gastroenteritis (defined as a change in stool consistency to loose or liquid form and/or an increase in frequency of evacuations (typically ≥ 3 in 24 hours) lasting no longer than 5 days

Szymanski 2019 *(Continued)*

	Exclusion criteria: use of antibiotics, gelatin tannate, diosmectite, probiotics, racecadotril, or zinc within a week before enrolment; exclusive breast-feeding; chronic diarrhoeal gastrointestinal disease; immunodeficiency disease; malnutrition Numbers completing study: 44/50 (88%) probiotic (5 LTFU; 1 excluded as mistaken randomization) and 47/50 (94%) control (3 LTFU)
Interventions	• *L reuteri* DSM 17938 2×10^8 colony-forming units (CFUs) daily for 5 days • Placebo once daily for 5 days Intervention started immediately after recruitment. All participants given standard rehydration therapy
Outcomes	• Duration of diarrhoea (time until normalization of stool consistency or normalization of number of stools and presence of normal stools for 48 hours) • Need for and duration of intravenous rehydration • Duration of hospitalization • Need for hospitalization of outpatients • Numbers of watery stools • Vomiting • Recurrence of diarrhoea (48 hours after intervention) • Severity of diarrhoea according to modified Vesikari Scale • Use of concomitant medications • Adverse events (whether or not they were considered to be related to study products)
Notes	Study location: Poland (low child and adult mortality) Cause of diarrhoea: rotavirus detected in 35/91 (38.5%) (18 (40.9%) probiotic and 17 (36.2%) placebo). Adenovirus detected in 2/91 (2.2%); *Salmonella enteritidis* in 2/91 (2.2%); unknown aetiology in 52/91 (57.1%) Nutritional status: severe malnutrition excluded Hydration status: 44 children (100%) in the probiotic arm and 44 (93.6%) in the control arm required intravenous fluids Source of funding: no external funding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization scheme
Allocation concealment (selection bias)	Unclear risk	No specific details of allocation concealment (and seemed to use fixed block size n = 6)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Researchers, caregivers, outcome assessors, and a person responsible for statistical analysis were blinded

Szymanski 2019 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	As above
Incomplete outcome data (attrition bias) All outcomes	High risk	Follow-up < 90% in intervention group
Selective reporting (reporting bias)	Low risk	Pre-defined primary outcome reported

Teran 2009

Study characteristics	
Methods	Randomized single-blind controlled trial; 1 centre Duration: 7 months (August 2007 to February 2008)
Participants	Inclusion criteria: inpatients; infants and children with history of acute watery diarrhoea (defined as ≥ 3 stools of liquid consistency/d < 72 hours' duration); positive for rotavirus and with moderate to severe dehydration Exclusion criteria: severe malnutrition; systemic infection requiring antibiotic therapy; severe chronic disease; identification of a second pathogen in the stool; ingestion of antibiotics, probiotics, or nitazoxanide 3 weeks before admission; recurrence of diarrhoea after discharge Numbers completing study: 25/30 (83.3%) probiotic; 25/31 (80.6%) control; 25/29 (86.2%) nitazoxanide. Patients with cause of diarrhoea other than rotavirus were withdrawn (probiotic group: 3 adenovirus, 2 *E histolytica*; control group: 3 *E histolytica,* 2 *Giardia*, 1 *S flexneri;* nitazoxanide group: 2 adenovirus, 1 *E histolytica, 1 Giardia*)
Interventions	Participants were allocated to 1 of 3 groups: a nitazoxanide group, a probiotic group, and a control group that received rehydration solutions only. Data from the probiotic group and from the control were used for this review • *L acidophilus, L rhamnosus, B longum, S boulardii (*total of *2*.5 × 10^9 organisms/d administered for an average of 4.2 days). Unclear if organisms were live or killed • Control (ORF only) Time when interventions started not described
Outcomes	• Duration of diarrhoea (time from admission until presence of first soft stool for at least 24 hours) • Stool number and consistency • Duration of fever • Vomiting • Duration of hospitalization No adverse events attributed to probiotic
Notes	Study location: Bolivia (high child and high adult mortality) Cause of diarrhoea: all rotavirus diarrhoea Nutritional status: severe malnutrition excluded; mild/moderate malnutrition in 5 (20%) probiotic and in 15 (60%) control Hydration status: all had moderate to severe dehydration; no further data presented

Teran 2009 *(Continued)*

Source of funding: research was not sponsored by any pharmaceutical company

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computerized admissions list
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Different dosing schedules
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcomes assessed by nursing staff; different interventions administered
Incomplete outcome data (attrition bias) All outcomes	High risk	Follow-up < 90%
Selective reporting (reporting bias)	Low risk	Pre-stated outcome reported

Urganci 2001

Study characteristics

Methods	Randomized controlled trial; 1 centre Duration: 1 year (June 200 to May 2001)
Participants	Inclusion criteria: consecutive inpatients aged 2 to 29 months with acute, non-bacterial diarrhoea (definition not stated) lasting > 48 hours able to receive oral medication Exclusion criteria: concomitant illness; antimicrobial, anti-diarrhoeal, or other drug affecting gut motility; severe electrolyte disturbance or dehydration Numbers completing study: 50 cases reported in both arms; numbers withdrawn because of deterioration in diarrhoea and concomitant disease requiring other drugs unclear
Interventions	• Lyophilized *Saccharomyces cerevisiae* Hansen CBS 5926 (250 mg daily in 5 mL cold liquid) • 250 mg glucose daily in 5 mL cold liquid Time of starting interventions and duration of administration not stated
Outcomes	Number of children cured at 48 hours Number of children cured at 96 hours: 42 (84%) probiotic vs 32 (64%) control; P < 0.05 Mean (SD) stool frequency on day 2 after treatment: 3.78 days (0.71) probiotic and 4.24 days (0.99) placebo (P < 0.01)

Urganci 2001 *(Continued)*

	Mean (SD) stool frequency on day 4 after treatment: 2.70 days (0.67) probiotic and 3.12 days (0.93) placebo ($P < 0.05$)
	No adverse events attributed to probiotic
Notes	Study location: Turkey (low child and adult mortality)
	Cause of diarrhoea: non-bacterial diarrhoea
	Nutritional status: no data presented
	Hydration status: none dehydrated
	Lactose intolerance identified in 8% in the probiotic group and in 26% in the placebo group
	Source of funding: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear who assessed outcomes
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Number of children withdrawn not stated
Selective reporting (reporting bias)	Low risk	Pre-stated outcome reported

Vidjeadevan 2018

Study characteristics

Methods	Single-blind randomized controlled trial; 1 centre
	Duration: 8 months (February to September 2017)
Participants	Inclusion criteria: children aged 6 months to 36 months; admitted to paediatric department with acute diarrhoea
	Exclusion criteria: blood in stools; clinical signs of a coexisting acute systemic illness like meningitis, sepsis, pneumonia; severely malnourished and immunocompromised children; prior probiotic or antibiotic drug administration; known hypersensitivity to probiotics

Vidjeadevan 2018 *(Continued)*

	Numbers completing study: 34/35 (97.1%) in *S boulardii* group (1 used antibiotics); 33/35 (94.3%) in *B clausii* group (1 used antibiotics, 1 LTFU); 32/35 (91.4%) in control group (2 used antibiotics, 1 LTFU)
Interventions	• *Saccharomyces boulardii*, dose and duration not stated (data extracted for probiotic group) • *Bacillus clausii*, dose and duration not stated Timing of start of intervention not stated All participants received oral rehydration solution and zinc
Outcomes	• Diarrhoea after 72 hours • Duration of diarrhoea • Duration of hosptial stay No comment regarding adverse events
Notes	Study location: India (high child and adult mortality) Cause of diarrhoea: bloody diarrhoea excluded Nutritional status: not stated Hydration status: not stated Source of funding: no funding sources Median duration of diarrhoea, hours (IQR): 72 (72 to 96) in *S boulardii* group, 96 (72 to 96) in *B clausii* group, and 108 (96-120) in control group. Not appropriate to convert median/IQR to mean/SD for duration of diarrhoea: small sample size and IQR for Group B either not correct or indicate skewed data

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization using permuted blocks
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study participants blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Single-blind study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up ≥ 90% in both groups
Selective reporting (reporting bias)	Low risk	All outcomes reported

Villarruel 2007

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

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random computer-generated into blocks of 20
Allocation concealment (selection bias)	Unclear risk	No specific details of allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical placebo

Villarruel 2007 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors blinded to intervention
Incomplete outcome data (attrition bias) All outcomes	High risk	Follow-up < 90% in both groups
Selective reporting (reporting bias)	Low risk	Pre-stated outcome reported

Vivatvakin 2006

Study characteristics	
Methods	Randomized open study; 1 centre Duration: 11 months (March 2003 to January 2004)
Participants	Inclusion criteria: inpatients and outpatients; infants and children with watery diarrhoea (not defined) for < 5 days Exclusion criteria: immunocompromised; suspected dysentery; diagnosed with persistent or chronic diarrhoea; chronic cardiac, pulmonary, or haematological illness; undergoing antibiotic treatment in the last 2 weeks; severe dehydration or shock 4/75 withdrawn (1 febrile seizure, 1 urinary tract infection, 2 with pneumonia); 2 participants were withdrawn from each group Numbers completing study: 36/38 (94.7%) probiotic; 35/37 (94.6%) control
Interventions	• Live *L acidophilus, Bifidobacterium infantis* (Infloran; 6×10^9 CFUs/d for 2 days) • Control group did not receive probiotic Timing of administration not stated
Outcomes	• Duration of diarrhoea • Weight change/d • Number of bowel motions on day 2 • Vomiting • Duration of hospitalization Duration of diarrhoea reported for rotavirus diarrhoea No adverse events attributed to probiotic
Notes	Location: Thailand; low child and adult mortality Cause of diarrhoea: suspected dysentery excluded; overall, 34% had rotavirus and 12.1% *Salmonella* in stools Nutritional status: no data presented Hydration status: severe dehydration excluded; mild/moderate dehydration in 25 (69.4%) probiotic and 23 (65.7%) control Source of funding: AIS donation fund, Thai Red Cross Society

Vivatvakin 2006 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not adequately described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up ≥ 90% in both groups
Selective reporting (reporting bias)	Low risk	Pre-stated outcome reported

Wunderlich 1989

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

Wunderlich 1989 *(Continued)*

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

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not adequately described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear who assessed outcomes
Incomplete outcome data (attrition bias) All outcomes	High risk	Follow-up < 90% in both groups
Selective reporting (reporting bias)	High risk	Primary outcome not pre-stated in methods

Xie 2013

Study characteristics

Methods	Randomized controlled trial; 1 centre Duration: 11 days
Participants	Inclusion criteria: infants with diarrhoea during autumn and winter; artificial feeding; first day of diarrhoea onset; loose stools; no mucus, pus, or blood in stools; rapid stool test of ELISA (Shenzhen Purcell Biotechnology Co., Ltd.) to detect rotavirus antigen positive; without any micro-agents and antibiotics before clinic Exclusion criteria: severe complications, such as severe dehydration, shock, pneumonia, etc.; patients' stool within pyocyte and erythrocyte, but to include patients with intestinal bacterial infection; treated with micro-ecological agents and antibiotics; breast-feeding during diarrhoea; change to lactose-free feeding during diarrhoea Numbers completing study: 50/50 (100%) probiotics; 50/50 (100%) control
Interventions	• Long-type *Bifidobacterium* and Bulgarian *Lactobacillus* 0.5 g, 3 times daily, duration unclear (not stated whether probiotic alive or killed) (data extracted for analysis) • Anti-rotavirus egg yolk immunoglobulin (IgY), 1 g 3 times daily (data not extracted for analysis) • Placebo (unclear contents), 3 times daily Intervention started on recruitment. Participants given basic treatment including oral montmorillonite powder and fluid replacement therapy and fed with customary milk powder

Xie 2013 *(Continued)*

Outcomes	• Clinical symptoms such as stool frequency and stool properties • Intestinal flora imbalance (detected and divided into 3 degrees by microscopic examination of stool) • Faecal SIgA level and faecal rotavirus shedding (measured by radioimmunoassay and double-antibody sandwich ELISA, respectively) No specific comment regarding adverse events
Notes	Study location: China (low child and adult mortality) Cause of diarrhoea: all rotavirus diarrhoea; bloody diarrhoea excluded Nutritional status: not stated Hydration status: not stated Source of funding: Youth Science Fund of Sichuan University (No. 2008053)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not adequately described
Allocation concealment (selection bias)	Unclear risk	Not adequately described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up ≥ 90% in both groups
Selective reporting (reporting bias)	Low risk	Pre-stated outcome reported

CFU: colony-forming units.
ED: emergency department.
ELISA: enzyme-linked immunosorbent assay.
IQR: interquartile ratio.
IV: intravenous.
NCHS: National Centre for Health Statistics.
ORF: oral rehydration fluid.
RCT: randomized controlled trial.
SD: standard deviation.
WHO: World Health Organization.

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

Study	Reason for exclusion
Agarwal 2001	No non-probiotic group. Participants included in Agarwal 2002 study
Agarwal 2002	No non-probiotic group
Ahmadipour 2018	Control group received zinc
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
Asmat 2018	No non-probiotic group
Barone 2000	No non-probiotic group
Beck 1961	Not a randomized controlled trial
Bellomo 1979	Cause of diarrhoea unclear. Additional treatment given to children with persisting diarrhoea
Bellomo 1980	No non-probiotic group. Study included children with diarrhoea secondary to antibiotic treatment or associated with respiratory infection
Bellomo 1982	Cause of diarrhoea unclear
Bin Li Xie 1995	Intervention groups not treated equally; antibacterials given to the non-probiotic group
Boulloche 1994	Killed probiotic
Brewster 2004	Secondary publication to Ritchie 2010
Camarri 1981	Intervention groups not treated equally; antibiotics given to the non-probiotic group
Cetina Sauri 1990	Secondary publication to Cetina-Sauri 1994
Chandra 2002	Prevention of rotavirus diarrhoea study
Chapoy 1985	Quasi-randomized: alternate allocation to study arms
Chicoine 1973	Unclear if acute diarrhoea
Costa-Ribeiro 2000a	Unclear whether a randomized controlled trial
Costa-Ribeiro 2000b	Prevention of diarrhoea study
Cui 2004	No non-probiotic group
Czerwionka 2009	No outcomes reported that can be included in this review
Dash 2016	Quasi-randomized
de dios Pozo-O 1978	Assessment of probiotic in prevention of traveller's diarrhoea
Eren 2010	No non-probiotic group
Escribano 2018	Prevention study

Study	Reason for exclusion
Fang 2009	Study of effect of probiotic on rotavirus shedding in stools; no diarrhoea outcomes reported
Fourrier 1968	No non-probiotic group
Freedman 2018b	Abstract preceding definitive trial report
Frigerio 1986	No efficacy data
Girola 1995	Children with gastroenteritis and antibiotic-associated diarrhoea studied together
Gracheva 1996	No non-probiotic group
Grandi 2009	No usable efficacy data
Grandy 2010	No outcomes reported that could be included in this review
Hafeez 2002	Quasi-randomized: allocation according to odd and even participant numbers
Henker 2007b	Secondary reference to Henker 2007a
Heydarian 2010	No non-probiotic group
Htwe 2008	Quasi-randomized: participants alternately assigned to intervention and control groups
Isolauri 1991	No non-probiotic group
Jimenez-Rodriguez 2018	No usable data to extract
Kaila 1992	No non-probiotic group
Kaila 1995	No non-probiotic group
Khan 2012	No outcomes reported that could be included in this review
Khanna 2005	Killed probiotic
Khoshdel 2018	Synbiotic evaluated
Korviakova 2000	Not a randomized controlled trial; probiotic vs antibiotic
Lahiri 2015a	No extractable data
Lahiri 2015b	No extractable data
Lei 2006	Probiotic used was not specified
Le Leyur 2010	Intervention group received an adapted lactose-free formula fortified with *S boulardii,* and control group received a standard formula; difference in diarrhoea outcomes between groups cannot be attributed to the probiotic
Lievin Le-Maol 2007	Killed probiotic
Lin 2009	Prevention study
Magreiter 2006	No non-probiotic control group

Study	Reason for exclusion
Majamaa 1995	No non-probiotic group
Maragkoudaki 2018	Intervention group received zinc in addition to probiotic
Maugo 2012	Unpublished MSc thesis
Mazo 2006	Prevention study
Michielutti 1995	Not a randomized controlled trial
Misra 2009	No outcomes reported that could be included in this review
Mitra 1990	No non-probiotic group
Moraes 2001	No non-probiotic group
Niv 1963	Not a randomized controlled trial; some children with diarrhoea thought to be caused by antibiotic treatment included
Ortlieb 1974	Participants with acute diarrhoea and antibiotic-associated diarrhoea combined
Pashapour 2006	Pasteurized yoghurt; likely killed probiotic
Pearce 1974	Intervention groups not treated equally; calcium carbonate given as placebo and may have reduced diarrhoea in the non-probiotic group
Pedone 1999	Prevention of diarrhoea study
Pedone 2000	Prevention of diarrhoea study
Pene 1966	No non-probiotic group; participants with diarrhoea of various causes (infectious, post-antibiotic) grouped together
Perez 2019	Included children with acute diarrhoea and children with antibiotic-associated diarrhoea
Pernica 2017	No usable efficacy data
Rafeey 2008b	Secondary publication to Rafeey 2008a
Rautanen 1998	No data for placebo group presented
Saint-Marc 1991	Not a randomized controlled trial; no non-probiotic group
Salazar-Lindo 2004	Mean duration of diarrhoea reported from responders only; children with ongoing diarrhoea excluded from analysis
Salazar-Lindo 2007	Active placebo
Satoh 1984	Not a randomized controlled trial; no non-probiotic group
Savas-Erdeve 2009	Study of amoebiasis-associated diarrhoea, not acute infectious diarrhoea
Schrezenmeir 2004	Antibiotic-associated diarrhoea included in the study
Sepp 1995	No usable efficacy data

Study	Reason for exclusion
Sharif 2017	Synbiotic evaluated and controls did not receive prebiotic
Simakachorn 2000	Killed probiotic
Sindhu 2014	Included children with chronic diarrhoea and with a recent history of yoghurt consumption
Singh 1987	No probiotic specified
Singh 2018	No control group
Sudarmo 2003	Other than the probiotic, unclear whether 2 intervention groups were treated the same. Probiotic group received high-lactose formula containing *B bifidum*. Unclear whether control group received high-lactose or normal formula
Sugita 1994	Quasi-ramdomized study
Szymanski 2005	Preliminary publication of Szymanski 2006
Táborská 1997	No efficacy data
Tojo 1987	Unclear whether diarrhoea acute and whether a randomized controlled trial
Urtula 2009	Unclear inclusion criteria
Zareen 2018	Intervention group received zinc in addition to probiotic

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

CTRI/2017/08/009543

Study name	Effect of probiotic *Bacillus clausii* UBBC07 in children with acute diarrhoea
Methods	RCT
Participants	Inclusion criteria • Children ≥ 6 months and ≤ 5 years of age • Clinical diagnosis of acute diarrhoea • More than 3 loose stools in the last 24 hours • No major illness Exclusion criteria • Children with severe malnutrition (weight for height < 3 SD of WHO charts) • Requiring antibiotics during the study period • Presence of severe diarrhoea that, in the opinion of the investigator, requires treatment other than investigational product and ORS • Presence of visible blood in the stool • Use of probiotics in the previous 3 weeks; use of antibiotics or any anti-diarrhoeal medication in the previous 3 weeks • Participated in any clinical trial or used any investigational product in the past 90 days • Known or expected hypersensitivity to any of the active substances or excipients

CTRI/2017/08/009543 *(Continued)*

	• Previous use (within 48 hours) of kaolin, pectin, bismuth subsalicylate, racecadotril, loperamide, atropine, and other anticholinergic agents
Interventions	• *Bacillus clausii* (BACIPRO) oral suspension containing *Bacillus clausii* UBBC07 - 2 billion CFUs/5 mL suspension. Dosage: 5 mL twice daily for 5 days • Placebo
Outcomes	Primary outcomes • Number and frequency of diarrhoea episodes post therapy • Duration of diarrhoea episodes post therapy • Consistency of stool Secondary outcomes • Clinical Global Impression - Improvement (CGI-I) by Investigator • Number, frequency, and duration of vomiting episodes • Number of fever episodes • Assessment of gut microbiota before and after treatment with probiotic • Number and frequency of required hospital admissions
Starting date	Registered 29 August 2017 (completed, not yet published)
Contact information	Dr DC Pandey; mvhrclko@gmail.com (principal investigator)
Notes	Location: India

CTRI/2018/04/013360

Study name	Efficacy of *Lactobacillus* sporogenes in treating acute diarrhoea in adults - randomized control study
Methods	RCT
Participants	Inclusion criteria • Patients older than 14 years who have acute diarrhoea Exclusion criteria • Serious complication (renal failure, metabolic acidosis, severe dehydration, hypovolaemic shock, heart failure) • History of allergy to *Lactobacillus* spp • History of diarrhoea caused by amoeba (as evidenced by demonstration of motile trophozoites with blood in stool) • Colorectal cancer (as diagnosed by a per rectal examination and/or endoscopic procedures where necessary) • Known allergy to study drugs • Patients who are already on probiotics
Interventions	• *Lactobacillus* sporogenes 120 million spores, 1 tablet containing 120 million spores of *Lactobacillus* sporogenes, 1 tablet thrice daily for 7 days • Placebo
Outcomes	Primary outcome

CTRI/2018/04/013360 *(Continued)*

	• Duration of diarrhoea Secondary outcome • Frequency of loose stools, abdominal pain, and hospital stay
Starting date	Registered 19 April 2018 (open to recruitment in July 2019)
Contact information	Meera Baby John; meerababyjohn@gmail.com (principal investigator)
Notes	Location: India

CTRI/2018/06/014480

Study name	A multicentric, randomized, placebo controlled double blind study to compare safety and tolerability of *Saccharomyces boulardii* in acute diarrhoea
Methods	RCT
Participants	Inclusion criteria • Aged 6 months to 5 years; of either gender; presenting with acute diarrhoea of ≤ 72 hours' duration without history of intake of any antibiotic and without dehydration or with features of mild or moderate dehydration Exclusion criteria • Clinical signs of dysentery, severe dehydration requiring hospitalization, or parenteral fluid therapy • Intake of any systemic antibiotic or any anti-diarrhoeal medication, in the 3 weeks before screening • Debilitated or seriously ill or immunocompromised • Symptoms or suspicion of an organic lesion of the digestive tract, or undiagnosed abdominal pain or rectal bleeding or other GI disorder, especially ulcerative colitis, Crohn's disease, history of carcinoma of the bowel, malabsorption syndrome, intolerance to certain food types (lactose), functional diarrhoea, and functional constipation • Use of probiotics in the 3 weeks before baseline visit • Current use of any drugs or treatments that are supposed to decrease gastrointestinal motility or any other concomitant anti-diarrhoeal medication • Have undergone ileostomy, jejunostomy, or colostomy • Hypersensitivity to any ingredient in the formulation • Coexisting features of acute systemic disease like septicaemia, meningitis, pneumonia, etc.
Interventions	• Gutgain: probiotic containing the yeast *Saccharomyces boulardii* and the bacterium *Bacillus subtilis* • Placebo
Outcomes	Primary outcomes • Duration of diarrhoea (time in hours after study product administration to last abnormal (loose or liquid) stool preceding normal stool output) • Stool frequency (number of times the participant passes stool every day) • Stool consistency (evaluated on a 4-point Likert scale) Secondary outcomes • Safety and tolerability of study medications

CTRI/2018/06/014480 *(Continued)*

	• Follow-up of participants in both groups up to 3 months post intervention to compare the incidence of acute diarrhoeal episodes between test and placebo groups
Starting date	Registered 8 June 2018 (not yet recruiting in July 2019)
Contact information	Dr Monjori Mitra; monjorimr@gmail.com (principal investigator)
Notes	Location: India

IRCT2017010312437N2

Study name	Evaluation of the effect of ORS with probiotics, zinc and vitamin A on diarrhea in children: a double blind clinical trial
Methods	RCT
Participants	Inclusion criteria • Age 1 to 5 years • Acute watery diarrhoea Exclusion criteria • High fever (T > 38.5° C) • Severe dehydration • Bloody diarrhoea • Severe malnutrition • Use of antibiotics or anti-diarrhoeal drugs • Having more than 1 complaint • Immune deficiency
Interventions	• 20 mg of zinc gluconate plus ORS in 4 sachets soluble in 250 mL of water daily • 20,000 IU vitamin A plus ORS in 4 sachets soluble in 250 mL of water daily • 109 CFU probiotics plus ORS in 4 sachets soluble in 250 mL of water daily • 20 mg of zinc gluconate, 20,000 IU vitamin A, 109 CFU probiotics plus ORS in 4 sachets soluble in 250 mL of water daily • ORS in 4 sachets soluble in 250 mL of water daily
Outcomes	• Duration of diarrhoea • Frequency of diarrhoea
Starting date	Registered 17 August 2017 (recruitment complete in July 2019)
Contact information	Mohsen Taghizadeh; taghizadeh-m@kaums.ac.ir
Notes	Location: Kashan, Iran

IRCT20170908128897N3

Study name	The effect of yeast probiotic (*Saccharomyces boulardii*) on acute diarrhoea in children
Methods	RCT

IRCT2017090812897N3 *(Continued)*

Participants	Inclusion criteria • Existence of acute diarrhoea • Mild and moderate dehydration • Age between 2 and 5 years • Failure to receive antibiotics and probiotic compounds in the past 1 month Exclusion criteria • Chronic diarrhoea • Malabsorption disease • Dysentery • Accompanying disease such as diabetes • Severe dehydration • Abdominal distension, suspected to intestinal obstruction • Vomiting
Interventions	• Cap Yomogi (contains 250 mg dried yeast *Saccharomyces boulardii*) as a single dose per day • Chickpea flour powder
Outcomes	Primary outcome • Frequency of diarrhoea Secondary outcome • Duration of diarrhoea
Starting date	Registered 7 October 2017 (recruitment complete in July 2019)
Contact information	Abolfazl Mahyar amahyar@qums.ac.ir
Notes	Location: Qazvin, Iran

ISRCTN18444252

Study name	Probiotics for treatment of acute childhood diarrhoea
Methods	RCT
Participants	Inclusion criteria • Infants and children with an episode of mild to moderate acute diarrhoea (> 4 (semi)-watery stools/d according to Bristol criteria (Bristol criteria ≥ 6)) lasting longer than 12 hours and less than 72 hours requiring hospitalization Exclusion criteria • Clinical features of hypovolaemic shock and/or necessitating admission to the intensive care unit • Taking immunosuppressive therapy • Known immunodeficiency disorder • Pancreatic dysfunction • Bloody diarrhoea • Chronic gastrointestinal disease • Short bowel syndrome • Bilious or bloody vomitus

ISRCTN18444252 *(Continued)*

	• Probiotics 1 month before admission • Severe malnutrition
Interventions	• Three combination probiotics containing 3 unique strains of bacteria: *Bifidobacterium lactis* Bi-07, *Lactobacillus rhamnosus* HN001, and *Lactobacillus acidophilus* NCFM. Given as a single sachet containing more than 10 billion colony-forming units (CFUs) once a day from the beginning of treatment for diarrhoea, for 7 days • No probiotic medication
Outcomes	Primary outcome • Duration of diarrhoea (time in hours from enrolment to last abnormal (loose or liquid) stool), measured using an appropriate CRF every day during the intervention Secondary outcome • Number of loose stools per day during the entire episode, measured using an appropriate CRF every day during the intervention
Starting date	1 November 2016 (completed, not yet published in July 2019)
Contact information	Dr Ke Chen, No. 1617 Riyue Avenue, Qingyang District, Chengdu, 610031, China
Notes	Location: Chengdu Women & Children's Central Hospital, China

NCT03539913

Study name	Efficacy and safety of probiotics in the treatment of acute gastroenteritis in children (SABINA)
Methods	Randomized parallel assignment trial
Participants	Inclusion criteria • Children of both genders aged between 6 months and 5 years • Presenting with acute diarrhoea (3 or more loose or liquid stools in a 24-hour period) since at least the last 24 hours but less than 5 days • Signed informed consent of legal representatives obtained before any study procedure • Parents who, according to the physician's opinion, are able to fill in the stool diary
Interventions	• *Saccharomyces boulardii* (Floratil), 250 mg sachets, twice daily (1 in the morning and 1 in the evening) during 5 consecutive days • *Bacillus clausii* (Enterogermina), 5 mL vials, twice daily (1 in the morning and 1 in the evening) during 5 consecutive days
Outcomes	Primary outcome • Efficacy of probiotics in reducing the duration of diarrhoea in children suffering from acute gastroenteritis Secondary outcomes • Efficacy of probiotics in improving the frequency and consistency of stools • Efficacy of probiotics in avoiding recurrence of diarrhoea • Effects of probiotics on disease severity • Safety and tolerability of studied probiotics

NCT03539913 *(Continued)*

Starting date	June 2017; completed June 2018
Contact information	Carine Francois (study director); contact information not provided
Notes	Location: Argentina

NCT03684538

Study name	Efficacy of probiotics vs zinc vs probiotics-zinc combination on acute diarrhea in children
Methods	RCT
Participants	Inclusion criteria • Acute diarrhoea • Parents signed informed consent • Have dehydration according to World Health Organization (WHO) clinical scale Exclusion criteria • Severe dehydration • Coexisting severe infection (e.g. sepsis, pneumonia, meningitis) • Immune deficiency • Parents refuse to provide written informed consent • Do not comply with treatment
Interventions	• Probiotics (*Saccharomyces boulardii*) 1 dose per day (250 mg) • Zinc (10 mg for participants younger than 6 months and 20 mg for older participants) 1 dose per day • Combination of probiotics (*Saccharomyces boulardii* 250 mg) with zinc (10 mg for participants younger than 6 months; 20 mg for older participants) 1 dose per day
Outcomes	Primary outcome • Diarrhea consistency (consistency of diarrhoea scored according to the "Bristol Stool Chart") Secondary outcomes • Diarrhoea duration (duration of diarrhoea in days) • Hospital stay (length of hospital stay in days)
Starting date	1 October 2018 (recruiting in July 2019)
Contact information	Mariam AlAbdullah A Rajab; drmariam1@hotmail.com (principal investigator)
Notes	Location: Makassed General Hospital, Beirut, Lebanon

CFU: colony-forming unit.
ORS: oral rehydration solution.
RCT: randomized controlled trial.
WHO: World Health Organization.

DATA AND ANALYSES

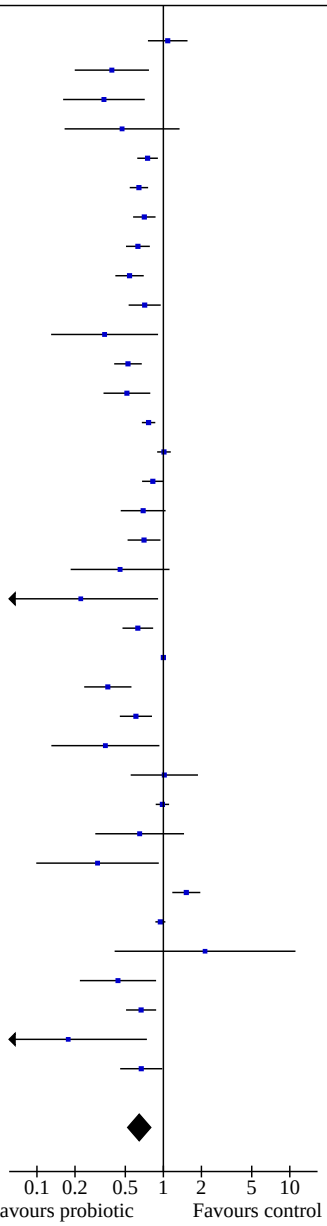
Comparison 1. Primary diarrhoea outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Diarrhoea lasting ≥ 48 hours	36	6053	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.52, 0.79]
1.2 Mean duration of diarrhoea	56	9138	Mean Difference (IV, Random, 95% CI)	-21.29 [-26.88, -15.71]

Analysis 1.1. Comparison 1: Primary diarrhoea outcomes, Outcome 1: Diarrhoea lasting ≥ 48 hours

Study or Subgroup	Probiotic Events	Probiotic Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Bhatnagar 1998	27	47	26	49	3.1%	1.08 [0.76 , 1.55]
Boudraa 2001	9	56	23	56	2.5%	0.39 [0.20 , 0.77]
Bruno 1981	6	25	17	24	2.4%	0.34 [0.16 , 0.71]
Bruno 1983	3	10	7	11	1.8%	0.47 [0.17 , 1.34]
Burki 2017	60	100	80	100	3.3%	0.75 [0.62 , 0.90]
Buydens 1996	57	93	88	92	3.3%	0.64 [0.54 , 0.76]
Cetina-Sauri 1994	41	65	58	65	3.3%	0.71 [0.58 , 0.87]
Chen 2010	64	150	97	143	3.3%	0.63 [0.51 , 0.78]
Correa 2011	39	90	69	86	3.2%	0.54 [0.42 , 0.70]
Costa-Ribeiro 2003	31	61	45	63	3.2%	0.71 [0.53 , 0.95]
D'Apuzzo 1982	4	21	10	18	2.0%	0.34 [0.13 , 0.91]
Dinleyici 2014	32	64	60	63	3.3%	0.53 [0.41 , 0.67]
Dinleyici 2015a	13	29	27	31	3.0%	0.51 [0.34 , 0.79]
Dinleyici 2015b	141	220	120	143	3.4%	0.76 [0.68 , 0.86]
Freedman 2018a	228	414	225	413	3.4%	1.01 [0.89 , 1.14]
Guandalini 2000	78	147	90	140	3.3%	0.83 [0.68 , 1.00]
Henker 2007a	21	55	32	58	3.0%	0.69 [0.46 , 1.04]
Henker 2008	34	75	49	76	3.2%	0.70 [0.52 , 0.95]
Hernandez 1998	5	25	11	25	2.1%	0.45 [0.18 , 1.12]
Isolauri 1994	2	21	9	21	1.3%	0.22 [0.05 , 0.91]
Jasinski 2002	25	45	46	52	3.2%	0.63 [0.48 , 0.83]
Javeed 2018	157	157	157	157	3.4%	1.00 [0.99 , 1.01]
Kurugol 2005	20	100	55	100	3.0%	0.36 [0.24 , 0.56]
Maity 2019	18	30	30	30	3.2%	0.61 [0.45 , 0.81]
Rerksuppaphol 2010	4	23	11	22	1.9%	0.35 [0.13 , 0.93]
Ritchie 2010	13	33	12	31	2.6%	1.02 [0.55 , 1.88]
Schnadower 2018	243	468	251	475	3.4%	0.98 [0.87 , 1.11]
Shornikova 1997b	6	21	11	25	2.3%	0.65 [0.29 , 1.46]
Shornikova 1997c	3	19	11	21	1.7%	0.30 [0.10 , 0.92]
Sirsat 2017	82	145	54	145	3.2%	1.52 [1.18 , 1.96]
Sudha 2019	54	59	58	60	3.4%	0.95 [0.86 , 1.04]
Szymanski 2019	4	44	2	47	1.1%	2.14 [0.41 , 11.09]
Teran 2009	7	25	16	25	2.5%	0.44 [0.22 , 0.88]
Urganci 2001	28	50	42	50	3.2%	0.67 [0.51 , 0.88]
Vivatvakin 2006	2	36	11	35	1.3%	0.18 [0.04 , 0.74]
Wunderlich 1989	19	40	27	38	3.1%	0.67 [0.46 , 0.98]
Total (95% CI)		**3063**		**2990**	**100.0%**	**0.64 [0.52 , 0.79]**
Total events:	1580		1937			

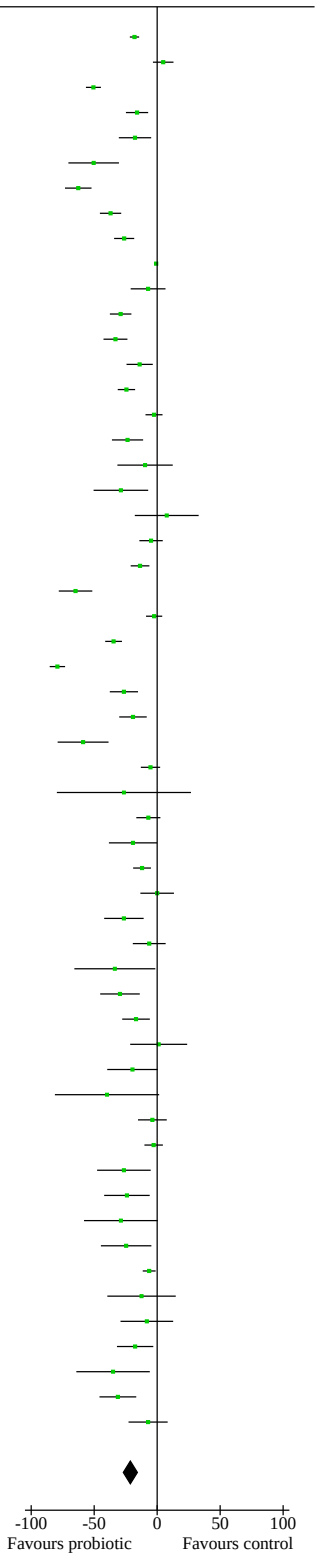
Heterogeneity: Tau² = 0.33; Chi² = 1531.30, df = 35 (P < 0.00001); I² = 98%
Test for overall effect: Z = 4.12 (P < 0.0001)
Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1: Primary diarrhoea outcomes, Outcome 2: Mean duration of diarrhoea

Study or Subgroup	Probiotic Mean	Probiotic SD	Probiotic Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Aggarwal 2014	60	13.3	100	78	13.3	100	2.1%	-18.00 [-21.69 , -14.31]
Basu 2007	163.2	50.4	323	158.4	55.2	323	2.0%	4.80 [-3.35 , 12.95]
Basu 2009	122.9	27.8	186	173.5	30.5	185	2.0%	-50.60 [-56.54 , -44.66]
Bhat 2018	41.68	10.84	40	57.65	26.31	40	2.0%	-15.97 [-24.79 , -7.15]
Boudraa 2001	44.1	33.7	56	61.7	35.6	56	1.9%	-17.60 [-30.44 , -4.76]
Burande 2013	81.6	33.6	35	132	50.4	35	1.6%	-50.40 [-70.47 , -30.33]
Burki 2017	77.52	31.42	100	140.16	43.54	100	1.9%	-62.64 [-73.16 , -52.12]
Canani 2007	78.5	35.52	100	115.5	23.53	92	2.0%	-37.00 [-45.46 , -28.54]
Chen 2010	60.1	31.7	150	86.3	37.6	143	2.0%	-26.20 [-34.18 , -18.22]
Costa-Ribeiro 2003	38.3	3.78	61	39.1	4.6	63	2.1%	-0.80 [-2.28 , 0.68]
Dalgic 2011	74.64	43.44	60	81.84	33.12	60	1.8%	-7.20 [-21.02 , 6.62]
Das 2016	60	11.85	30	89	20	28	2.0%	-29.00 [-37.54 , -20.46]
Dinleyici 2014	70.7	26.1	64	103.8	28.4	63	2.0%	-33.10 [-42.59 , -23.61]
Dinleyici 2015a	60.4	24.5	29	74.3	15.3	31	1.9%	-13.90 [-24.32 , -3.48]
Dinleyici 2015b	75.4	33.1	220	99.8	32.5	143	2.0%	-24.40 [-31.29 , -17.51]
Dutta 2011	34	20.4	78	36.5	21.4	70	2.0%	-2.50 [-9.25 , 4.25]
El-Soud 2015	74.88	22.08	25	98.4	22.56	25	1.9%	-23.52 [-35.89 , -11.15]
Erdogan 2012	158.4	40.8	25	168	38.4	25	1.6%	-9.60 [-31.56 , 12.36]
Francavilla 2012	50.4	40.8	35	79.2	50.4	34	1.6%	-28.80 [-50.47 , -7.13]
Freedman 2015	71.1	78.3	61	63.5	64.3	62	1.5%	7.60 [-17.74 , 32.94]
Freedman 2018a	67.35	65.99	414	72.2	69.99	413	2.0%	-4.85 [-14.12 , 4.42]
Guandalini 2000	58.3	27.6	147	71.9	35.8	140	2.0%	-13.60 [-21.02 , -6.18]
Guarino 1997	76.8	34.61	52	141.6	33.26	48	1.9%	-64.80 [-78.10 , -51.50]
Hamid 2019	76.8	31.2	160	79.2	26.4	150	2.0%	-2.40 [-8.82 , 4.02]
Henker 2007a	70.3	23.52	55	104.9	9.12	58	2.0%	-34.60 [-41.24 , -27.96]
Henker 2008	57.6	19.47	75	136.8	18.8	76	2.0%	-79.20 [-85.31 , -73.09]
Huang 2014	43.2	38.4	82	69.6	33.6	77	1.9%	-26.40 [-37.60 , -15.20]
Isolauri 1994	36	16.8	21	55.2	19.2	21	1.9%	-19.20 [-30.11 , -8.29]
Jasinski 2002	74.6	47.76	45	133.4	53.76	52	1.6%	-58.80 [-79.00 , -38.60]
Javeed 2018	104.9	33.1	157	110.2	36.1	157	2.0%	-5.30 [-12.96 , 2.36]
Kianifar 2009	81.6	108.6	32	108	105.2	30	0.7%	-26.40 [-79.63 , 26.83]
Kowalska-Duplaga 2004	54.6	30	86	61.6	34	87	2.0%	-7.00 [-16.55 , 2.55]
Kurugol 2005	112.8	60	100	132	76.8	100	1.7%	-19.20 [-38.30 , -0.10]
Lee 2001	74.4	16.8	50	86.4	19.2	50	2.0%	-12.00 [-19.07 , -4.93]
Mao 2008	67.2	40.2	70	67.2	40.5	71	1.9%	0.00 [-13.32 , 13.32]
Narayanappa 2008	104.4	30.05	40	130.8	40.66	40	1.8%	-26.40 [-42.07 , -10.73]
Nixon 2012	67.7	36	63	74	39.5	66	1.9%	-6.30 [-19.33 , 6.73]
Pant 1996	45.6	14.4	14	79.2	55.2	12	1.2%	-33.60 [-65.73 , -1.47]
Park 2017	105.12	30.96	28	134.64	29.52	29	1.8%	-29.52 [-45.23 , -13.81]
Riaz 2012	49.55	23.72	43	66.34	29.27	47	1.9%	-16.79 [-27.76 , -5.82]
Ritchie 2010	52.4	49.8	33	51.2	42.4	31	1.5%	1.20 [-21.42 , 23.82]
Rosenfeldt 2002a	81.5	37.3	30	101.1	47.6	39	1.6%	-19.60 [-39.63 , 0.43]
Rosenfeldt 2002b	75.9	39.7	24	115.7	85	19	1.0%	-39.80 [-81.19 , 1.59]
Sarkar 2005	90.4	45	115	94.2	43.3	115	1.9%	-3.80 [-15.21 , 7.61]
Schnadower 2018	60.74	58.88	468	63.53	55.73	475	2.0%	-2.79 [-10.11 , 4.53]
Shornikova 1997a	64.8	52.8	59	91.2	67.2	64	1.6%	-26.40 [-47.67 , -5.13]
Shornikova 1997b	36	26.4	21	60	36	25	1.7%	-24.00 [-42.07 , -5.93]
Shornikova 1997c	40.8	38.4	19	69.6	55.2	21	1.3%	-28.80 [-58.05 , 0.45]
Simadibrata 2013	58.74	38.54	38	83.37	49.83	38	1.6%	-24.63 [-44.66 , -4.60]
Sudha 2019	75.25	12.96	59	81.6	15.43	60	2.0%	-6.35 [-11.47 , -1.23]
Szymanski 2006	83.6	55.6	46	96	71.5	41	1.4%	-12.40 [-39.55 , 14.75]
Szymanski 2019	58.7	43.8	44	66.9	57.4	47	1.6%	-8.20 [-29.10 , 12.70]
Teran 2009	57.1	25.4	25	74.6	26.6	25	1.8%	-17.50 [-31.92 , -3.08]
Villarruel 2007	112.8	46.56	35	147.8	76.8	37	1.3%	-35.00 [-64.16 , -5.84]
Vivatvakin 2006	38.4	16.8	36	69.6	40.8	35	1.8%	-31.20 [-45.79 , -16.61]
Xie 2013	132	38.4	50	139.2	40.8	50	1.8%	-7.20 [-22.73 , 8.33]
Total (95% CI)			**4614**			**4524**	**100.0%**	**-21.29 [-26.88 , -15.71]**

Heterogeneity: Tau² = 390.92; Chi² = 1283.22, df = 55 (P < 0.00001); I² = 96%
Test for overall effect: Z = 7.48 (P < 0.00001)
Test for subgroup differences: Not applicable



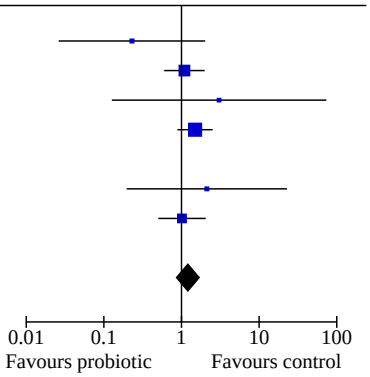
Comparison 2. Secondary diarrhoea outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Number of people hospitalized in community studies	7	2333	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.86, 1.69]
2.2 Duration of hospitalization in inpatient studies	24	4056	Mean Difference (IV, Random, 95% CI)	-18.03 [-27.28, -8.78]
2.3 Diarrhoea lasting ≥ 14 days	9	2928	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.16, 1.53]

Analysis 2.1. Comparison 2: Secondary diarrhoea outcomes, Outcome 1: Number of people hospitalized in community studies

Study or Subgroup	Probiotic Events	Probiotic Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Canani 2007	1	100	4	92	2.4%	0.23 [0.03 , 2.02]
Erdogan 2012	12	25	11	25	30.9%	1.09 [0.60 , 1.99]
Freedman 2015	1	61	0	62	1.1%	3.05 [0.13 , 73.40]
Freedman 2018a	33	414	22	413	41.1%	1.50 [0.89 , 2.52]
Maity 2019	0	30	0	30		Not estimable
Nixon 2012	2	67	1	71	2.0%	2.12 [0.20 , 22.83]
Schnadower 2018	15	468	15	475	22.6%	1.01 [0.50 , 2.05]
Total (95% CI)		**1165**		**1168**	**100.0%**	**1.21 [0.86 , 1.69]**
Total events:	64		53			

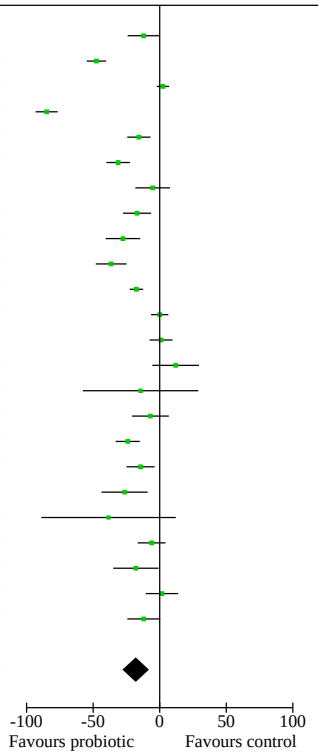
Heterogeneity: Tau² = 0.00; Chi² = 3.77, df = 5 (P = 0.58); I² = 0%
Test for overall effect: Z = 1.10 (P = 0.27)
Test for subgroup differences: Not applicable



Analysis 2.2. Comparison 2: Secondary diarrhoea outcomes, Outcome 2: Duration of hospitalization in inpatient studies

Study or Subgroup	Probiotic Mean	Probiotic SD	Probiotic Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Aggarwal 2014	80	13.41	9	92.14	15.54	14	4.3%	-12.14 [-24.10 , -0.18]
Azim 2014	74.16	11.04	45	121.68	22.32	45	4.5%	-47.52 [-54.80 , -40.24]
Basu 2007	223.2	31.2	323	220.8	28.8	323	4.6%	2.40 [-2.23 , 7.03]
Basu 2009	149.04	29.76	186	234	49.44	185	4.5%	-84.96 [-93.27 , -76.65]
Bhat 2018	65.23	10.17	40	80.85	26.42	40	4.5%	-15.62 [-24.39 , -6.85]
Chen 2010	69.6	19.2	150	100.8	50.4	143	4.5%	-31.20 [-40.01 , -22.39]
Dalgic 2011	98.64	39.36	60	103.92	33.12	60	4.3%	-5.28 [-18.30 , 7.74]
Das 2016	74	19.26	30	91	21.48	28	4.4%	-17.00 [-27.53 , -6.47]
Dinleyici 2014	103.44	31.2	64	131.04	42.48	63	4.3%	-27.60 [-40.58 , -14.62]
Dinleyici 2015b	110.4	41.28	148	146.88	41.04	72	4.3%	-36.48 [-48.06 , -24.90]
Guandalini 2000	78.8	22.2	147	96.3	21.4	140	4.6%	-17.50 [-22.54 , -12.46]
Hamid 2019	91.2	33.6	160	91.2	24	150	4.5%	0.00 [-6.47 , 6.47]
Hong Chau 2018	79	37.04	143	78	37.78	147	4.5%	1.00 [-7.61 , 9.61]
Huang 2014	136.8	57.6	82	124.8	55.2	77	4.0%	12.00 [-5.53 , 29.53]
Kianifar 2009	50.4	95.04	32	64.8	78.87	30	2.3%	-14.40 [-57.77 , 28.97]
Kowalska-Duplaga 2004	113	33	86	120	57	87	4.2%	-7.00 [-20.86 , 6.86]
Kurugol 2005	69.6	28.8	100	93.6	36	100	4.5%	-24.00 [-33.04 , -14.96]
Rafeey 2008a	81.6	21.6	40	96	26.4	40	4.4%	-14.40 [-24.97 , -3.83]
Rosenfeldt 2002a	38.4	24	30	64.8	48	39	4.0%	-26.40 [-43.74 , -9.06]
Shornikova 1997a	182.4	134.4	59	220.8	151.2	64	1.9%	-38.40 [-88.88 , 12.08]
Szymanski 2019	61.4	21.49	44	67.5	27.92	44	4.4%	-6.10 [-16.51 , 4.31]
Teran 2009	83	33.7	25	100.9	27.3	25	4.0%	-17.90 [-34.90 , -0.90]
Vidjeadevan 2018	81.84	24.96	34	80.16	25.44	32	4.3%	1.68 [-10.49 , 13.85]
Vivatvakin 2006	50.4	28.8	36	62.4	24	35	4.3%	-12.00 [-24.32 , 0.32]
Total (95% CI)			**2073**			**1983**	**100.0%**	**-18.03 [-27.28 , -8.78]**

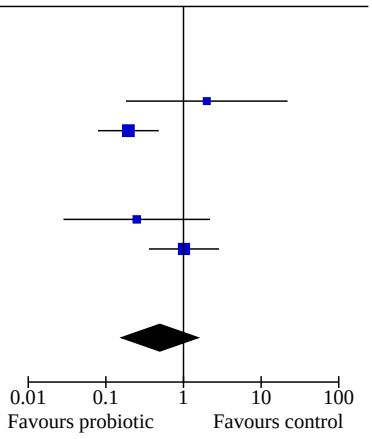
Heterogeneity: Tau² = 478.55; Chi² = 493.36, df = 23 (P < 0.00001); I² = 95%
Test for overall effect: Z = 3.82 (P = 0.0001)
Test for subgroup differences: Not applicable



Analysis 2.3. Comparison 2: Secondary diarrhoea outcomes, Outcome 3: Diarrhoea lasting ≥ 14 days

Study or Subgroup	Probiotic Events	Probiotic Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Buydens 1996	0	93	0	92		Not estimable
Costa-Ribeiro 2003	0	61	0	63		Not estimable
Freedman 2018a	2	414	1	413	14.9%	2.00 [0.18 , 21.92]
Henker 2008	5	75	26	76	35.3%	0.19 [0.08 , 0.48]
Javeed 2018	0	157	0	157		Not estimable
Khan 2017	0	48	0	48		Not estimable
Kurugol 2005	1	100	4	100	17.0%	0.25 [0.03 , 2.20]
Schnadower 2018	7	468	7	475	32.8%	1.01 [0.36 , 2.87]
Villarruel 2007	0	44	0	44		Not estimable
Total (95% CI)		**1460**		**1468**	**100.0%**	**0.49 [0.16 , 1.53]**
Total events:	15		38			

Heterogeneity: Tau² = 0.73; Chi² = 7.43, df = 3 (P = 0.06); I² = 60%
Test for overall effect: Z = 1.22 (P = 0.22)
Test for subgroup differences: Not applicable

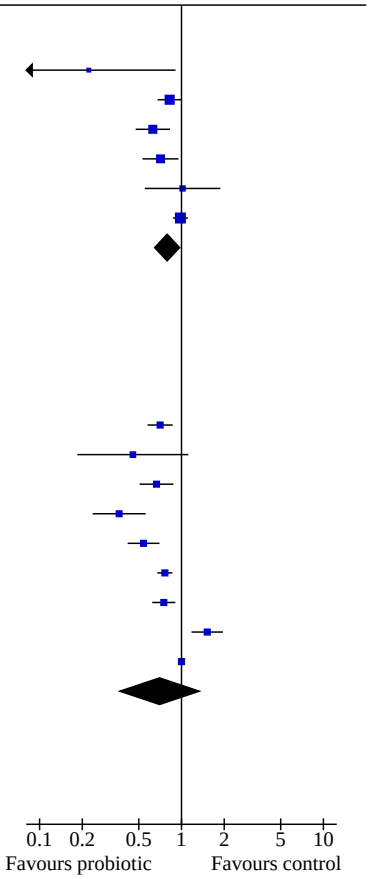


Comparison 3. Strain of probiotic organisms

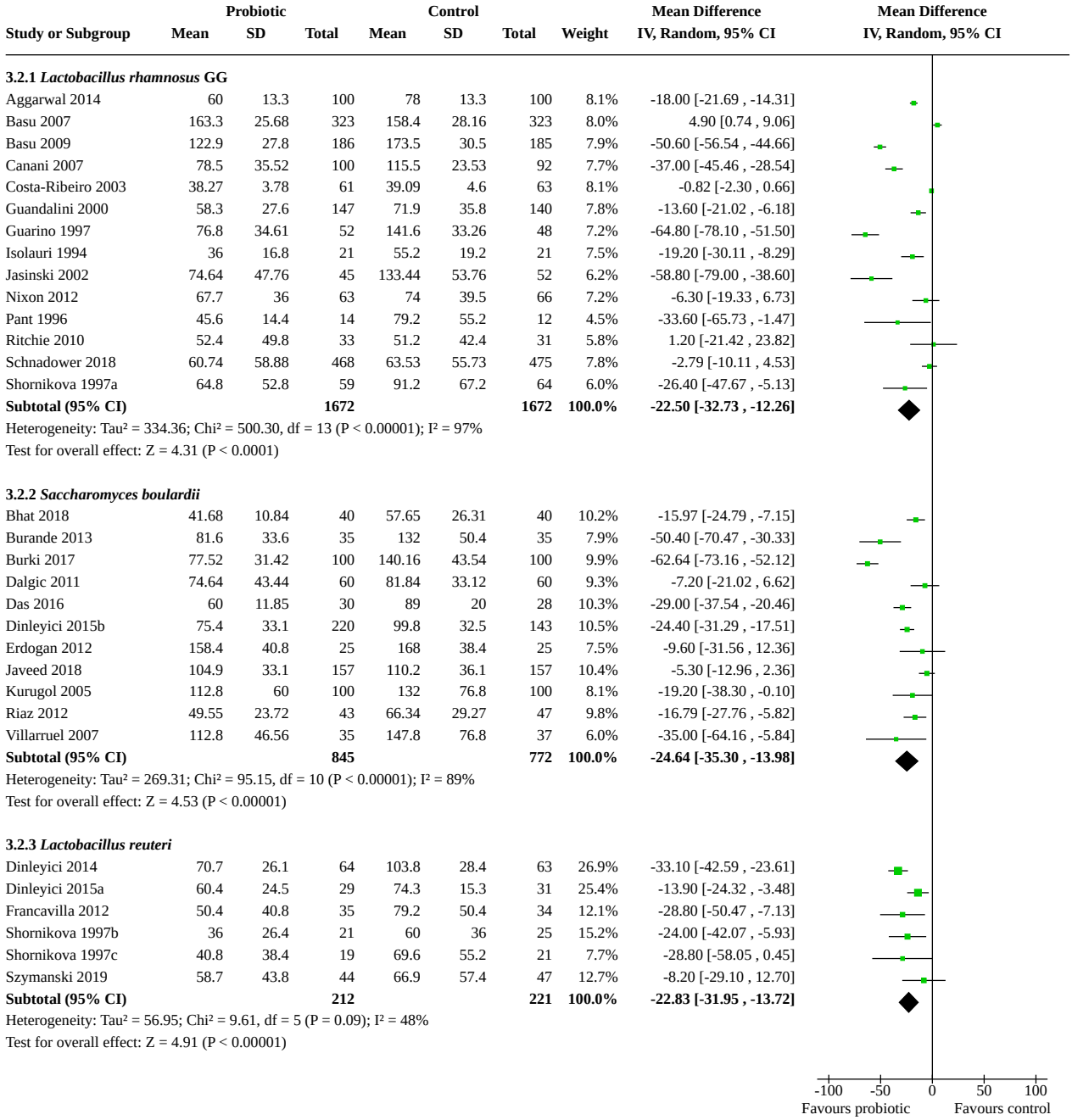
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Diarrhoea lasting ≥ 48 hours	15		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1.1 *Lactobacillus rhamnosus* GG	6	1557	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.65, 0.97]
3.1.2 *Saccharomyces boulardii*	9	1823	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.37, 1.33]
3.2 Mean duration of diarrhoea	31		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.2.1 *Lactobacillus rhamnosus* GG	14	3344	Mean Difference (IV, Random, 95% CI)	-22.50 [-32.73, -12.26]
3.2.2 *Saccharomyces boulardii*	11	1617	Mean Difference (IV, Random, 95% CI)	-24.64 [-35.30, -13.98]
3.2.3 *Lactobacillus reuteri*	6	433	Mean Difference (IV, Random, 95% CI)	-22.83 [-31.95, -13.72]

Analysis 3.1. Comparison 3: Strain of probiotic organisms, Outcome 1: Diarrhoea lasting ≥ 48 hours

Study or Subgroup	Probiotic Events	Probiotic Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
3.1.1 *Lactobacillus rhamnosus* GG						
Isolauri 1994	2	21	9	21	1.9%	0.22 [0.05 , 0.91]
Guandalini 2000	78	147	90	140	24.0%	0.83 [0.68 , 1.00]
Jasinski 2002	25	45	46	52	19.5%	0.63 [0.48 , 0.83]
Costa-Ribeiro 2003	31	61	45	63	18.8%	0.71 [0.53 , 0.95]
Ritchie 2010	13	33	12	31	8.1%	1.02 [0.55 , 1.88]
Schnadower 2018	243	468	251	475	27.8%	0.98 [0.87 , 1.11]
Subtotal (95% CI)		**775**		**782**	**100.0%**	**0.79 [0.65 , 0.97]**
Total events:	392		453			
Heterogeneity: Tau² = 0.03; Chi² = 15.06, df = 5 (P = 0.01); I² = 67%						
Test for overall effect: Z = 2.26 (P = 0.02)						
3.1.2 *Saccharomyces boulardii*						
Cetina-Sauri 1994	41	65	58	65	11.4%	0.71 [0.58 , 0.87]
Hernandez 1998	5	25	11	25	9.4%	0.45 [0.18 , 1.12]
Urganci 2001	28	50	42	50	11.3%	0.67 [0.51 , 0.88]
Kurugol 2005	20	100	55	100	11.0%	0.36 [0.24 , 0.56]
Correa 2011	39	90	69	86	11.3%	0.54 [0.42 , 0.70]
Dinleyici 2015b	141	220	120	143	11.5%	0.76 [0.68 , 0.86]
Burki 2017	60	100	80	100	11.4%	0.75 [0.62 , 0.90]
Sirsat 2017	82	145	54	145	11.3%	1.52 [1.18 , 1.96]
Javeed 2018	157	157	157	157	11.5%	1.00 [0.99 , 1.01]
Subtotal (95% CI)		**952**		**871**	**100.0%**	**0.70 [0.37 , 1.33]**
Total events:	573		646			
Heterogeneity: Tau² = 0.94; Chi² = 1212.91, df = 8 (P < 0.00001); I² = 99%						
Test for overall effect: Z = 1.08 (P = 0.28)						



Analysis 3.2. Comparison 3: Strain of probiotic organisms, Outcome 2: Mean duration of diarrhoea



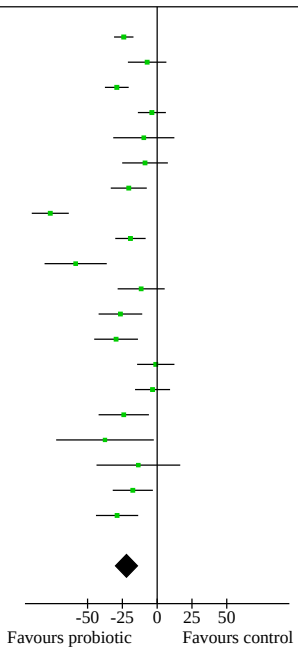
Comparison 4. Diarrhoea pathogen: rotavirus

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Mean duration of diarrhoea	20	1414	Mean Difference (IV, Random, 95% CI)	-22.06 [-29.93, -14.18]

Analysis 4.1. Comparison 4: Diarrhoea pathogen: rotavirus, Outcome 1: Mean duration of diarrhoea

Study or Subgroup	Probiotic Mean	Probiotic SD	Probiotic Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Aggarwal 2014	60	8.89	21	84	13.33	20	6.0%	-24.00 [-30.97 , -17.03]
Dalgic 2011	74.64	43.44	60	81.84	33.12	60	5.3%	-7.20 [-21.02 , 6.62]
Das 2016	60	11.85	30	89	20	28	5.9%	-29.00 [-37.54 , -20.46]
Dutta 2011	28.7	18.8	25	32.5	17.8	26	5.8%	-3.80 [-13.86 , 6.26]
Erdogan 2012	158.4	40.8	25	168	38.4	25	4.2%	-9.60 [-31.56 , 12.36]
Freedman 2018a	62.55	52.07	116	71.27	60.75	79	5.0%	-8.72 [-25.13 , 7.69]
Guandalini 2000	56.2	16.9	56	76.6	41.6	45	5.4%	-20.40 [-33.34 , -7.46]
Guarino 1997	72	26.7	31	148.8	26.3	30	5.4%	-76.80 [-90.10 , -63.50]
Isolauri 1994	36	16.8	21	55.2	19.2	21	5.7%	-19.20 [-30.11 , -8.29]
Jasinski 2002	62.64	35.04	18	121.2	36	21	4.2%	-58.56 [-80.90 , -36.22]
Kowalska-Duplaga 2004	52	26	31	63.5	34	22	4.9%	-11.50 [-28.40 , 5.40]
Narayanappa 2008	104.4	30.05	40	130.8	40.66	40	5.1%	-26.40 [-42.07 , -10.73]
Park 2017	105.12	30.96	28	134.64	29.52	29	5.1%	-29.52 [-45.23 , -13.81]
Sarkar 2005	94	43	75	95	37.9	65	5.4%	-1.00 [-14.40 , 12.40]
Schnadower 2018	48.3	37.38	74	51.61	36.26	59	5.5%	-3.31 [-15.89 , 9.27]
Shornikova 1997b	36	26.4	21	60	36	25	4.8%	-24.00 [-42.07 , -5.93]
Szymanski 2006	77.5	35.4	22	115	66.9	17	2.8%	-37.50 [-72.57 , -2.43]
Szymanski 2019	52.5	32.9	18	66	54.6	17	3.3%	-13.50 [-43.58 , 16.58]
Teran 2009	57.1	25.4	25	74.6	26.6	25	5.2%	-17.50 [-31.92 , -3.08]
Vivatvakin 2006	40.8	14.4	15	69.6	19.2	8	5.1%	-28.80 [-43.97 , -13.63]
Total (95% CI)			**752**			**662**	**100.0%**	**-22.06 [-29.93 , -14.18]**

Heterogeneity: Tau² = 254.32; Chi² = 122.18, df = 19 (P < 0.00001); I² = 84%
Test for overall effect: Z = 5.49 (P < 0.00001)
Test for subgroup differences: Not applicable

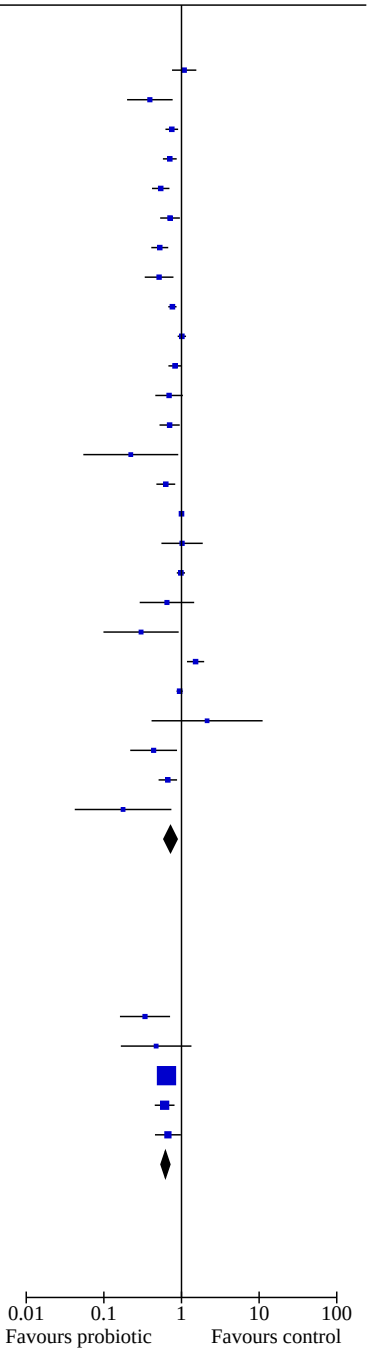


Comparison 5. Age of participants

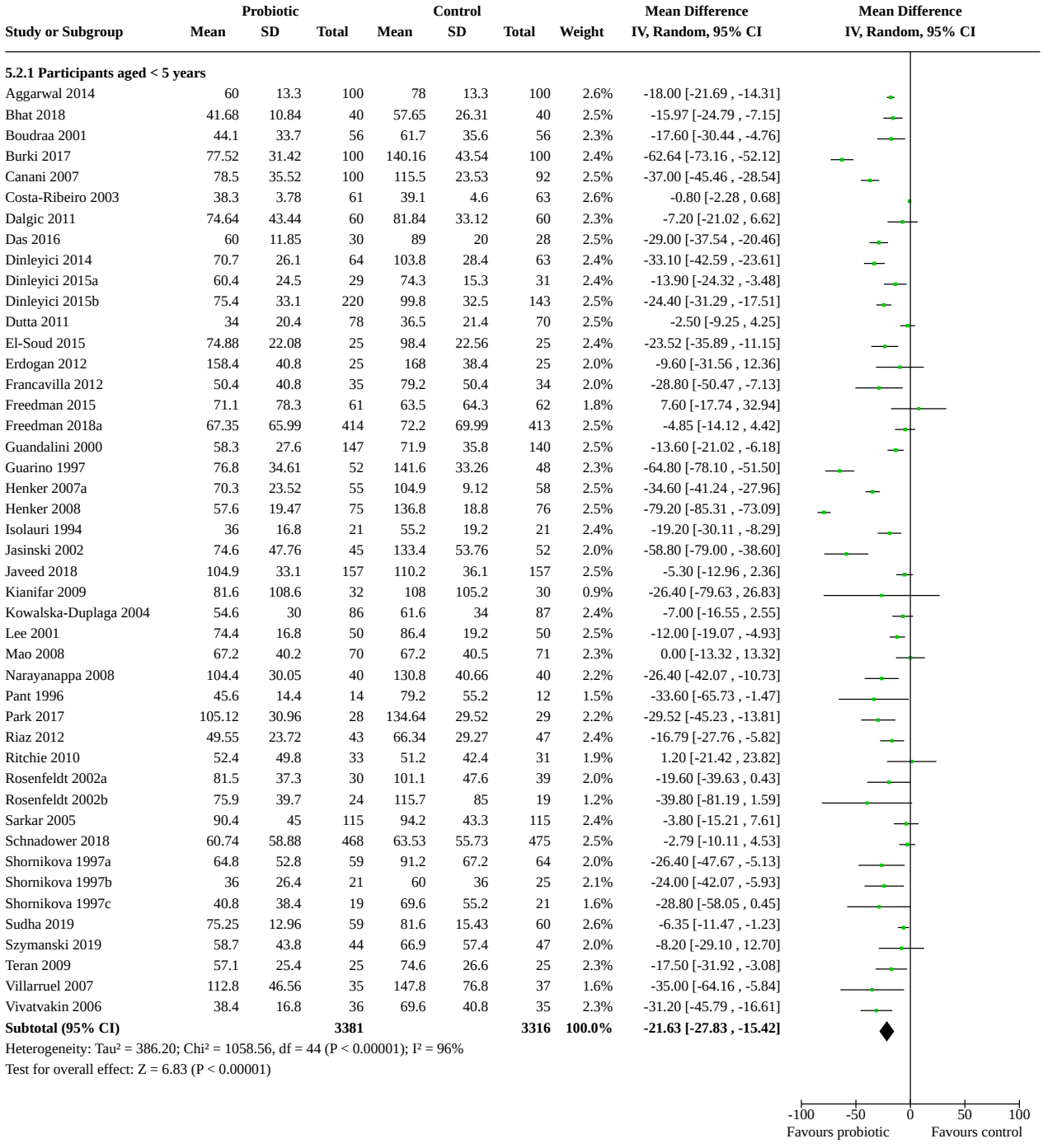
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Diarrhoea lasting ≥ 48 hours	31		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1.1 Participants aged < 5 years	26	5033	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.59, 0.88]
5.1.2 Participants aged ≥ 18 years	5	393	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.54, 0.71]
5.2 Mean duration of diarrhoea	45		Mean Difference (IV, Random, 95% CI)	Subtotals only
5.2.1 Participants aged < 5 years	45	6697	Mean Difference (IV, Random, 95% CI)	-21.63 [-27.83, -15.42]

Analysis 5.1. Comparison 5: Age of participants, Outcome 1: Diarrhoea lasting ≥ 48 hours

Study or Subgroup	Probiotic Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
5.1.1 Participants aged < 5 years						
Bhatnagar 1998	27	47	26	49	4.2%	1.08 [0.76 , 1.55]
Boudraa 2001	9	56	23	56	3.1%	0.39 [0.20 , 0.77]
Burki 2017	60	100	80	100	4.7%	0.75 [0.62 , 0.90]
Cetina-Sauri 1994	41	65	58	65	4.7%	0.71 [0.58 , 0.87]
Correa 2011	39	90	69	86	4.5%	0.54 [0.42 , 0.70]
Costa-Ribeiro 2003	31	61	45	63	4.4%	0.71 [0.53 , 0.95]
Dinleyici 2014	32	64	60	63	4.5%	0.53 [0.41 , 0.67]
Dinleyici 2015a	13	29	27	31	4.0%	0.51 [0.34 , 0.79]
Dinleyici 2015b	141	220	120	143	4.8%	0.76 [0.68 , 0.86]
Freedman 2018a	228	414	225	413	4.8%	1.01 [0.89 , 1.14]
Guandalini 2000	78	147	90	140	4.7%	0.83 [0.68 , 1.00]
Henker 2007a	21	55	32	58	4.1%	0.69 [0.46 , 1.04]
Henker 2008	34	75	49	76	4.4%	0.70 [0.52 , 0.95]
Isolauri 1994	2	21	9	21	1.4%	0.22 [0.05 , 0.91]
Jasinski 2002	25	45	46	52	4.5%	0.63 [0.48 , 0.83]
Javeed 2018	157	157	157	157	4.9%	1.00 [0.99 , 1.01]
Ritchie 2010	13	33	12	31	3.3%	1.02 [0.55 , 1.88]
Schnadower 2018	243	468	251	475	4.8%	0.98 [0.87 , 1.11]
Shornikova 1997b	6	21	11	25	2.7%	0.65 [0.29 , 1.46]
Shornikova 1997c	3	19	11	21	1.9%	0.30 [0.10 , 0.92]
Sirsat 2017	82	145	54	145	4.5%	1.52 [1.18 , 1.96]
Sudha 2019	54	59	58	60	4.9%	0.95 [0.86 , 1.04]
Szymanski 2019	4	44	2	47	1.1%	2.14 [0.41 , 11.09]
Teran 2009	7	25	16	25	3.1%	0.44 [0.22 , 0.88]
Urganci 2001	28	50	42	50	4.5%	0.67 [0.51 , 0.88]
Vivatvakin 2006	2	36	11	35	1.4%	0.18 [0.04 , 0.74]
Subtotal (95% CI)		**2546**		**2487**	**100.0%**	**0.72 [0.59 , 0.88]**
Total events:	1380		1584			
Heterogeneity: Tau² = 0.21; Chi² = 829.10, df = 25 (P < 0.00001); I² = 97%						
Test for overall effect: Z = 3.22 (P = 0.001)						
5.1.2 Participants aged ≥ 18 years						
Bruno 1981	6	25	17	24	3.2%	0.34 [0.16 , 0.71]
Bruno 1983	3	10	7	11	1.6%	0.47 [0.17 , 1.34]
Buydens 1996	57	93	88	92	62.8%	0.64 [0.54 , 0.76]
Maity 2019	18	30	30	30	20.5%	0.61 [0.45 , 0.81]
Wunderlich 1989	19	40	27	38	11.9%	0.67 [0.46 , 0.98]
Subtotal (95% CI)		**198**		**195**	**100.0%**	**0.62 [0.54 , 0.71]**
Total events:	103		169			
Heterogeneity: Tau² = 0.00; Chi² = 3.33, df = 4 (P = 0.50); I² = 0%						
Test for overall effect: Z = 7.04 (P < 0.00001)						



Analysis 5.2. Comparison 5: Age of participants, Outcome 2: Mean duration of diarrhoea



Study or Subgroup	Probiotic Mean	Probiotic SD	Probiotic Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
5.2.1 Participants aged < 5 years								
Aggarwal 2014	60	13.3	100	78	13.3	100	2.6%	-18.00 [-21.69 , -14.31]
Bhat 2018	41.68	10.84	40	57.65	26.31	40	2.5%	-15.97 [-24.79 , -7.15]
Boudraa 2001	44.1	33.7	56	61.7	35.6	56	2.3%	-17.60 [-30.44 , -4.76]
Burki 2017	77.52	31.42	100	140.16	43.54	100	2.4%	-62.64 [-73.16 , -52.12]
Canani 2007	78.5	35.52	100	115.5	23.53	92	2.5%	-37.00 [-45.46 , -28.54]
Costa-Ribeiro 2003	38.3	3.78	61	39.1	4.6	63	2.6%	-0.80 [-2.28 , 0.68]
Dalgic 2011	74.64	43.44	60	81.84	33.12	60	2.3%	-7.20 [-21.02 , 6.62]
Das 2016	60	11.85	30	89	20	28	2.5%	-29.00 [-37.54 , -20.46]
Dinleyici 2014	70.7	26.1	64	103.8	28.4	63	2.4%	-33.10 [-42.59 , -23.61]
Dinleyici 2015a	60.4	24.5	29	74.3	15.3	31	2.4%	-13.90 [-24.32 , -3.48]
Dinleyici 2015b	75.4	33.1	220	99.8	32.5	143	2.5%	-24.40 [-31.29 , -17.51]
Dutta 2011	34	20.4	78	36.5	21.4	70	2.5%	-2.50 [-9.25 , 4.25]
El-Soud 2015	74.88	22.08	25	98.4	22.56	25	2.4%	-23.52 [-35.89 , -11.15]
Erdogan 2012	158.4	40.8	25	168	38.4	25	2.0%	-9.60 [-31.56 , 12.36]
Francavilla 2012	50.4	40.8	35	79.2	50.4	34	2.0%	-28.80 [-50.47 , -7.13]
Freedman 2015	71.1	78.3	61	63.5	64.3	62	1.8%	7.60 [-17.74 , 32.94]
Freedman 2018a	67.35	65.99	414	72.2	69.99	413	2.5%	-4.85 [-14.12 , 4.42]
Guandalini 2000	58.3	27.6	147	71.9	35.8	140	2.5%	-13.60 [-21.02 , -6.18]
Guarino 1997	76.8	34.61	52	141.6	33.26	48	2.3%	-64.80 [-78.10 , -51.50]
Henker 2007a	70.3	23.52	55	104.9	9.12	58	2.5%	-34.60 [-41.24 , -27.96]
Henker 2008	57.6	19.47	75	136.8	18.8	76	2.5%	-79.20 [-85.31 , -73.09]
Isolauri 1994	36	16.8	21	55.2	19.2	21	2.4%	-19.20 [-30.11 , -8.29]
Jasinski 2002	74.6	47.76	45	133.4	53.76	52	2.0%	-58.80 [-79.00 , -38.60]
Javeed 2018	104.9	33.1	157	110.2	36.1	157	2.5%	-5.30 [-12.96 , 2.36]
Kianifar 2009	81.6	108.6	32	108	105.2	30	0.9%	-26.40 [-79.63 , 26.83]
Kowalska-Duplaga 2004	54.6	30	86	61.6	34	87	2.4%	-7.00 [-16.55 , 2.55]
Lee 2001	74.4	16.8	50	86.4	19.2	50	2.5%	-12.00 [-19.07 , -4.93]
Mao 2008	67.2	40.2	70	67.2	40.5	71	2.3%	0.00 [-13.32 , 13.32]
Narayanappa 2008	104.4	30.05	40	130.8	40.66	40	2.2%	-26.40 [-42.07 , -10.73]
Pant 1996	45.6	14.4	14	79.2	55.2	12	1.5%	-33.60 [-65.73 , -1.47]
Park 2017	105.12	30.96	28	134.64	29.52	29	2.2%	-29.52 [-45.23 , -13.81]
Riaz 2012	49.55	23.72	43	66.34	29.27	47	2.4%	-16.79 [-27.76 , -5.82]
Ritchie 2010	52.4	49.8	33	51.2	42.4	31	1.9%	1.20 [-21.42 , 23.82]
Rosenfeldt 2002a	81.5	37.3	30	101.1	47.6	39	2.0%	-19.60 [-39.63 , 0.43]
Rosenfeldt 2002b	75.9	39.7	24	115.7	85	19	1.2%	-39.80 [-81.19 , 1.59]
Sarkar 2005	90.4	45	115	94.2	43.3	115	2.4%	-3.80 [-15.21 , 7.61]
Schnadower 2018	60.74	58.88	468	63.53	55.73	475	2.5%	-2.79 [-10.11 , 4.53]
Shornikova 1997a	64.8	52.8	59	91.2	67.2	64	2.0%	-26.40 [-47.67 , -5.13]
Shornikova 1997b	36	26.4	21	60	36	25	2.1%	-24.00 [-42.07 , -5.93]
Shornikova 1997c	40.8	38.4	19	69.6	55.2	21	1.6%	-28.80 [-58.05 , 0.45]
Sudha 2019	75.25	12.96	59	81.6	15.43	60	2.6%	-6.35 [-11.47 , -1.23]
Szymanski 2019	58.7	43.8	44	66.9	57.4	47	2.0%	-8.20 [-29.10 , 12.70]
Teran 2009	57.1	25.4	25	74.6	26.6	25	2.3%	-17.50 [-31.92 , -3.08]
Villarruel 2007	112.8	46.56	35	147.8	76.8	37	1.6%	-35.00 [-64.16 , -5.84]
Vivatvakin 2006	38.4	16.8	36	69.6	40.8	35	2.3%	-31.20 [-45.79 , -16.61]
Subtotal (95% CI)			**3381**			**3316**	**100.0%**	**-21.63 [-27.83 , -15.42]**

Heterogeneity: Tau² = 386.20; Chi² = 1058.56, df = 44 (P < 0.00001); I² = 96%
Test for overall effect: Z = 6.83 (P < 0.00001)

Comparison 6. Severity of diarrhoea (inpatient vs outpatient)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Diarrhoea lasting ≥ 48 hours	21		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

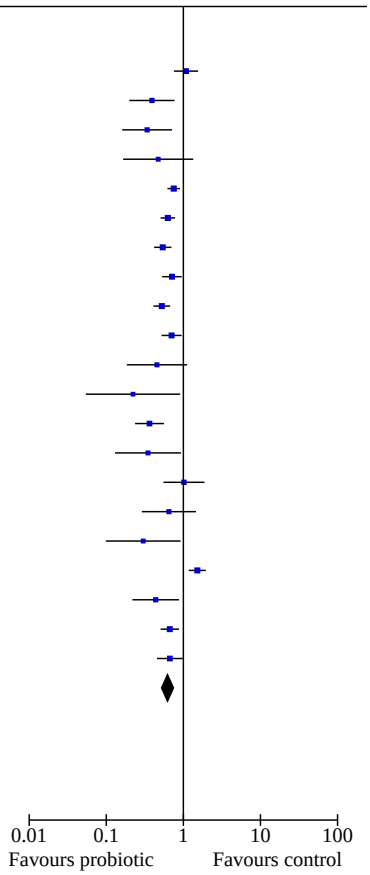
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1.1 Inpatient	21	2354	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.52, 0.74]
6.2 Mean duration of diarrhoea	44		Mean Difference (IV, Random, 95% CI)	Subtotals only
6.2.1 Inpatient	36	5071	Mean Difference (IV, Random, 95% CI)	-21.71 [-29.72, -13.70]
6.2.2 Outpatient	8	828	Mean Difference (IV, Random, 95% CI)	-28.55 [-43.09, -14.01]

Analysis 6.1. Comparison 6: Severity of diarrhoea (inpatient vs outpatient), Outcome 1: Diarrhoea lasting ≥ 48 hours

Study or Subgroup	Probiotic Events	Probiotic Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
6.1.1 Inpatient						
Bhatnagar 1998	27	47	26	49	6.0%	1.08 [0.76 , 1.55]
Boudraa 2001	9	56	23	56	3.7%	0.39 [0.20 , 0.77]
Bruno 1981	6	25	17	24	3.3%	0.34 [0.16 , 0.71]
Bruno 1983	3	10	7	11	2.1%	0.47 [0.17 , 1.34]
Burki 2017	60	100	80	100	7.4%	0.75 [0.62 , 0.90]
Chen 2010	64	150	97	143	7.2%	0.63 [0.51 , 0.78]
Correa 2011	39	90	69	86	6.8%	0.54 [0.42 , 0.70]
Costa-Ribeiro 2003	31	61	45	63	6.6%	0.71 [0.53 , 0.95]
Dinleyici 2014	32	64	60	63	6.9%	0.53 [0.41 , 0.67]
Henker 2008	34	75	49	76	6.5%	0.70 [0.52 , 0.95]
Hernandez 1998	5	25	11	25	2.6%	0.45 [0.18 , 1.12]
Isolauri 1994	2	21	9	21	1.3%	0.22 [0.05 , 0.91]
Kurugol 2005	20	100	55	100	5.4%	0.36 [0.24 , 0.56]
Rerksuppaphol 2010	4	23	11	22	2.3%	0.35 [0.13 , 0.93]
Ritchie 2010	13	33	12	31	4.1%	1.02 [0.55 , 1.88]
Shornikova 1997b	6	21	11	25	3.0%	0.65 [0.29 , 1.46]
Shornikova 1997c	3	19	11	21	1.9%	0.30 [0.10 , 0.92]
Sirsat 2017	82	145	54	145	6.9%	1.52 [1.18 , 1.96]
Teran 2009	7	25	16	25	3.6%	0.44 [0.22 , 0.88]
Urganci 2001	28	50	42	50	6.7%	0.67 [0.51 , 0.88]
Wunderlich 1989	19	40	27	38	5.8%	0.67 [0.46 , 0.98]
Subtotal (95% CI)		**1180**		**1174**	**100.0%**	**0.62 [0.52 , 0.74]**
Total events:	494		732			

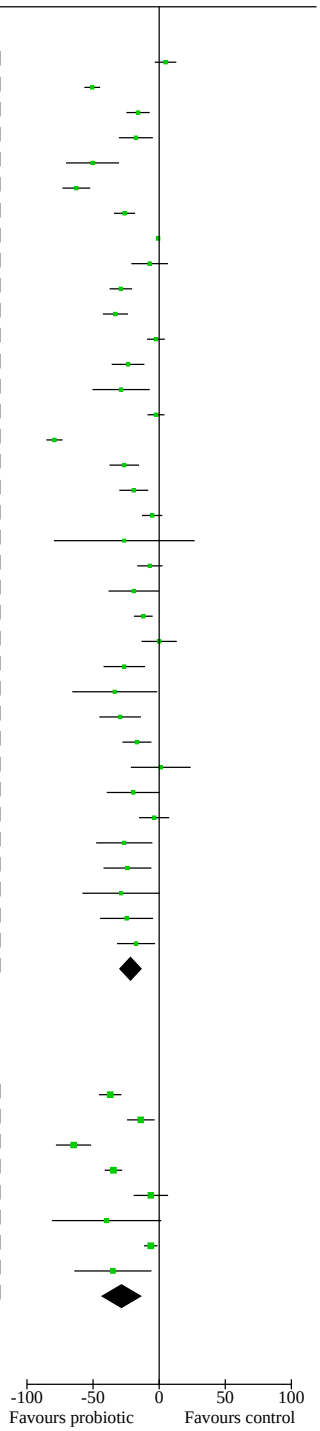
Heterogeneity: Tau² = 0.10; Chi² = 78.48, df = 20 (P < 0.00001); I² = 75%

Test for overall effect: Z = 5.27 (P < 0.00001)



Analysis 6.2. Comparison 6: Severity of diarrhoea (inpatient vs outpatient), Outcome 2: Mean duration of diarrhoea

Study or Subgroup	Probiotic Mean	Probiotic SD	Probiotic Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
6.2.1 Inpatient								
Basu 2007	163.2	50.4	323	158.4	55.2	323	3.0%	4.80 [-3.35 , 12.95]
Basu 2009	122.9	27.8	186	173.5	30.5	185	3.1%	-50.60 [-56.54 , -44.66]
Bhat 2018	41.68	10.84	40	57.65	26.31	40	3.0%	-15.97 [-24.79 , -7.15]
Boudraa 2001	44.1	33.7	56	61.7	35.6	56	2.9%	-17.60 [-30.44 , -4.76]
Burande 2013	81.6	33.6	35	132	50.4	35	2.6%	-50.40 [-70.47 , -30.33]
Burki 2017	77.52	31.42	100	140.16	43.54	100	2.9%	-62.64 [-73.16 , -52.12]
Chen 2010	60.1	31.7	150	86.3	37.6	143	3.0%	-26.20 [-34.18 , -18.22]
Costa-Ribeiro 2003	38.3	3.78	61	39.1	4.6	63	3.1%	-0.80 [-2.28 , 0.68]
Dalgic 2011	74.64	43.44	60	81.84	33.12	60	2.8%	-7.20 [-21.02 , 6.62]
Das 2016	60	11.85	30	89	20	28	3.0%	-29.00 [-37.54 , -20.46]
Dinleyici 2014	70.7	26.1	64	103.8	28.4	63	3.0%	-33.10 [-42.59 , -23.61]
Dutta 2011	34	20.4	78	36.5	21.4	70	3.0%	-2.50 [-9.25 , 4.25]
El-Soud 2015	74.88	22.08	25	98.4	22.56	25	2.9%	-23.52 [-35.89 , -11.15]
Francavilla 2012	50.4	40.8	35	79.2	50.4	34	2.5%	-28.80 [-50.47 , -7.13]
Hamid 2019	76.8	31.2	160	79.2	26.4	150	3.0%	-2.40 [-8.82 , 4.02]
Henker 2008	57.6	19.47	75	136.8	18.8	76	3.0%	-79.20 [-85.31 , -73.09]
Huang 2014	43.2	38.4	82	69.6	33.6	77	2.9%	-26.40 [-37.60 , -15.20]
Isolauri 1994	36	16.8	21	55.2	19.2	21	2.9%	-19.20 [-30.11 , -8.29]
Javeed 2018	104.9	33.1	157	110.2	36.1	157	3.0%	-5.30 [-12.96 , 2.36]
Kianifar 2009	81.6	108.6	32	108	105.2	30	1.3%	-26.40 [-79.63 , 26.83]
Kowalska-Duplaga 2004	54.6	30	86	61.6	34	87	3.0%	-7.00 [-16.55 , 2.55]
Kurugol 2005	112.8	60	100	132	76.8	100	2.6%	-19.20 [-38.30 , -0.10]
Lee 2001	74.4	16.8	50	86.4	19.2	50	3.0%	-12.00 [-19.07 , -4.93]
Mao 2008	67.2	40.2	70	67.2	40.5	71	2.9%	0.00 [-13.32 , 13.32]
Narayanappa 2008	104.4	30.05	40	130.8	40.66	40	2.8%	-26.40 [-42.07 , -10.73]
Pant 1996	45.6	14.4	14	79.2	55.2	12	2.1%	-33.60 [-65.73 , -1.47]
Park 2017	105.12	30.96	28	134.64	29.52	29	2.8%	-29.52 [-45.23 , -13.81]
Riaz 2012	49.55	23.72	43	66.34	29.27	47	2.9%	-16.79 [-27.76 , -5.82]
Ritchie 2010	52.4	49.8	33	51.2	42.4	31	2.5%	1.20 [-21.42 , 23.82]
Rosenfeldt 2002a	81.5	37.3	30	101.1	47.6	39	2.6%	-19.60 [-39.63 , 0.43]
Sarkar 2005	90.4	45	115	94.2	43.3	115	2.9%	-3.80 [-15.21 , 7.61]
Shornikova 1997a	64.8	52.8	59	91.2	67.2	64	2.5%	-26.40 [-47.67 , -5.13]
Shornikova 1997b	36	26.4	21	60	36	25	2.7%	-24.00 [-42.07 , -5.93]
Shornikova 1997c	40.8	38.4	19	69.6	55.2	21	2.2%	-28.80 [-58.05 , 0.45]
Simadibrata 2013	58.74	38.54	38	83.37	49.83	38	2.6%	-24.63 [-44.66 , -4.60]
Teran 2009	57.1	25.4	25	74.6	26.6	25	2.8%	-17.50 [-31.92 , -3.08]
Subtotal (95% CI)			**2541**			**2530**	**100.0%**	**-21.71 [-29.72 , -13.70]**
Heterogeneity: Tau² = 538.45; Chi² = 1066.23, df = 35 (P < 0.00001); I² = 97%								
Test for overall effect: Z = 5.31 (P < 0.00001)								
6.2.2 Outpatient								
Canani 2007	78.5	35.52	100	115.5	23.53	92	14.2%	-37.00 [-45.46 , -28.54]
Dinleyici 2015a	60.4	24.5	29	74.3	15.3	31	13.9%	-13.90 [-24.32 , -3.48]
Guarino 1997	76.8	34.61	52	141.6	33.26	48	13.3%	-64.80 [-78.10 , -51.50]
Henker 2007a	70.3	23.52	55	104.9	9.12	58	14.5%	-34.60 [-41.24 , -27.96]
Nixon 2012	67.7	36	63	74	39.5	66	13.3%	-6.30 [-19.33 , 6.73]
Rosenfeldt 2002b	75.9	39.7	24	115.7	85	19	6.8%	-39.80 [-81.19 , 1.59]
Sudha 2019	75.25	12.96	59	81.6	15.43	60	14.7%	-6.35 [-11.47 , -1.23]
Villarruel 2007	112.8	46.56	35	147.8	76.8	37	9.3%	-35.00 [-64.16 , -5.84]
Subtotal (95% CI)			**417**			**411**	**100.0%**	**-28.55 [-43.09 , -14.01]**
Heterogeneity: Tau² = 368.22; Chi² = 110.95, df = 7 (P < 0.00001); I² = 94%								
Test for overall effect: Z = 3.85 (P = 0.0001)								

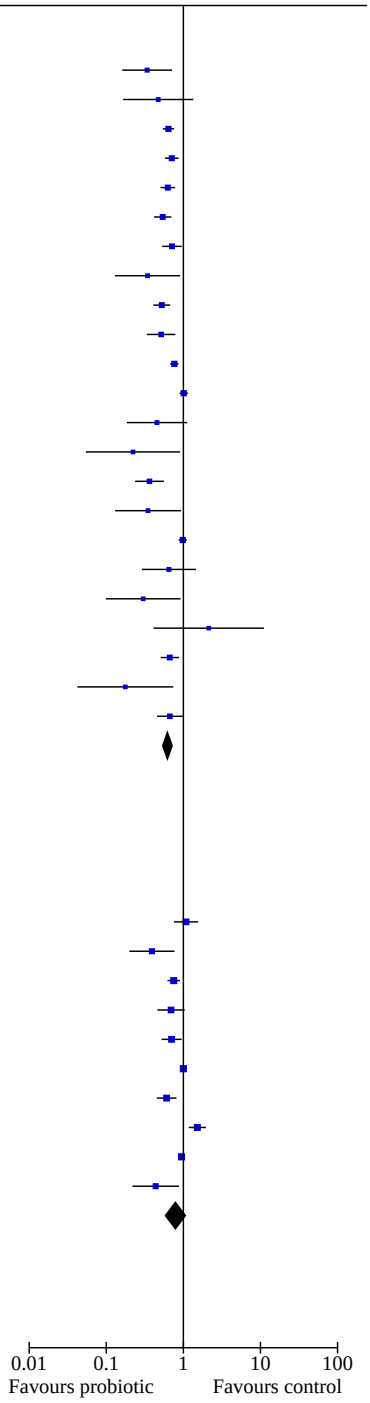


Comparison 7. Country mortality stratum

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Diarrhoea lasting ≥ 48 hours	33		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1.1 Child and adult mortality low or very low	23	4100	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.54, 0.71]
7.1.2 Child or adult mortality high	10	1505	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.59, 1.06]
7.2 Mean duration of diarrhoea	53		Mean Difference (IV, Random, 95% CI)	Subtotals only
7.2.1 Child and adult mortality low or very low	34	5225	Mean Difference (IV, Random, 95% CI)	-19.18 [-24.98, -13.39]
7.2.2 Child or adult mortality high	19	3465	Mean Difference (IV, Random, 95% CI)	-24.05 [-35.28, -12.83]

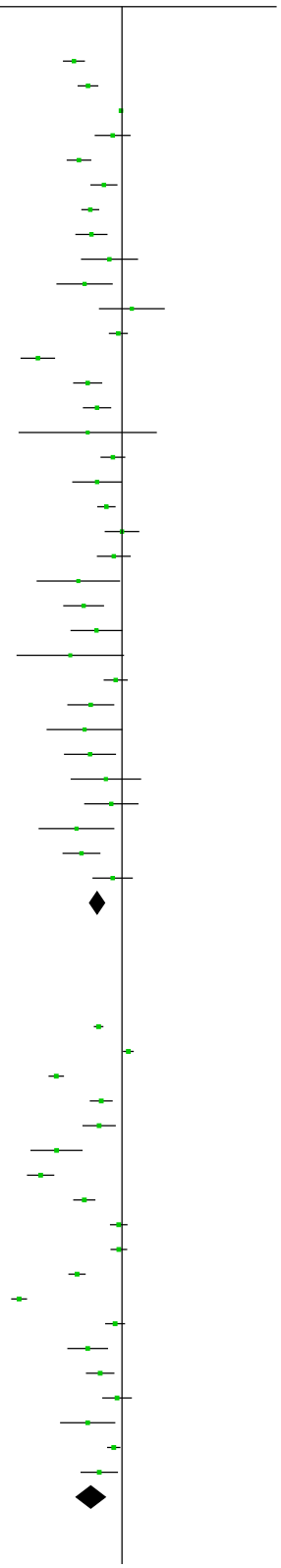
Analysis 7.1. Comparison 7: Country mortality stratum, Outcome 1: Diarrhoea lasting ≥ 48 hours

Study or Subgroup	Probiotic Events	Probiotic Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
7.1.1 Child and adult mortality low or very low						
Bruno 1981	6	25	17	24	2.5%	0.34 [0.16 , 0.71]
Bruno 1983	3	10	7	11	1.5%	0.47 [0.17 , 1.34]
Buydens 1996	57	93	88	92	7.4%	0.64 [0.54 , 0.76]
Cetina-Sauri 1994	41	65	58	65	7.1%	0.71 [0.58 , 0.87]
Chen 2010	64	150	97	143	6.9%	0.63 [0.51 , 0.78]
Correa 2011	39	90	69	86	6.5%	0.54 [0.42 , 0.70]
Costa-Ribeiro 2003	31	61	45	63	6.1%	0.71 [0.53 , 0.95]
D'Apuzzo 1982	4	21	10	18	1.7%	0.34 [0.13 , 0.91]
Dinleyici 2014	32	64	60	63	6.6%	0.53 [0.41 , 0.67]
Dinleyici 2015a	13	29	27	31	4.7%	0.51 [0.34 , 0.79]
Dinleyici 2015b	141	220	120	143	7.8%	0.76 [0.68 , 0.86]
Freedman 2018a	228	414	225	413	7.8%	1.01 [0.89 , 1.14]
Hernandez 1998	5	25	11	25	1.9%	0.45 [0.18 , 1.12]
Isolauri 1994	2	21	9	21	0.9%	0.22 [0.05 , 0.91]
Kurugol 2005	20	100	55	100	4.7%	0.36 [0.24 , 0.56]
Rerksuppaphol 2010	4	23	11	22	1.7%	0.35 [0.13 , 0.93]
Schnadower 2018	243	468	251	475	7.8%	0.98 [0.87 , 1.11]
Shornikova 1997b	6	21	11	25	2.2%	0.65 [0.29 , 1.46]
Shornikova 1997c	3	19	11	21	1.3%	0.30 [0.10 , 0.92]
Szymanski 2019	4	44	2	47	0.7%	2.14 [0.41 , 11.09]
Urganci 2001	28	50	42	50	6.3%	0.67 [0.51 , 0.88]
Vivatvakin 2006	2	36	11	35	0.9%	0.18 [0.04 , 0.74]
Wunderlich 1989	19	40	27	38	5.1%	0.67 [0.46 , 0.98]
Subtotal (95% CI)		**2089**		**2011**	**100.0%**	**0.62 [0.54 , 0.71]**
Total events:	995		1264			
Heterogeneity: Tau² = 0.06; Chi² = 98.85, df = 22 (P < 0.00001); I² = 78%						
Test for overall effect: Z = 6.62 (P < 0.00001)						
7.1.2 Child or adult mortality high						
Bhatnagar 1998	27	47	26	49	10.0%	1.08 [0.76 , 1.55]
Boudraa 2001	9	56	23	56	7.3%	0.39 [0.20 , 0.77]
Burki 2017	60	100	80	100	11.2%	0.75 [0.62 , 0.90]
Henker 2007a	21	55	32	58	9.6%	0.69 [0.46 , 1.04]
Henker 2008	34	75	49	76	10.4%	0.70 [0.52 , 0.95]
Javeed 2018	157	157	157	157	11.7%	1.00 [0.99 , 1.01]
Maity 2019	18	30	30	30	10.5%	0.61 [0.45 , 0.81]
Sirsat 2017	82	145	54	145	10.7%	1.52 [1.18 , 1.96]
Sudha 2019	54	59	58	60	11.5%	0.95 [0.86 , 1.04]
Teran 2009	7	25	16	25	7.1%	0.44 [0.22 , 0.88]
Subtotal (95% CI)		**749**		**756**	**100.0%**	**0.79 [0.59 , 1.06]**
Total events:	469		525			
Heterogeneity: Tau² = 0.20; Chi² = 315.20, df = 9 (P < 0.00001); I² = 97%						
Test for overall effect: Z = 1.56 (P = 0.12)						



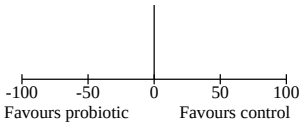
Analysis 7.2. Comparison 7: Country mortality stratum, Outcome 2: Mean duration of diarrhoea

Study or Subgroup	Probiotic Mean	Probiotic SD	Probiotic Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
7.2.1 Child and adult mortality low or very low								
Canani 2007	78.5	35.52	100	115.5	23.53	92	3.6%	-37.00 [-45.46 , -28.54]
Chen 2010	60.1	31.7	150	86.3	37.6	143	3.7%	-26.20 [-34.18 , -18.22]
Costa-Ribeiro 2003	38.3	3.78	61	39.1	4.6	63	3.9%	-0.80 [-2.28 , 0.68]
Dalgic 2011	74.64	43.44	60	81.84	33.12	60	3.2%	-7.20 [-21.02 , 6.62]
Dinleyici 2014	70.7	26.1	64	103.8	28.4	63	3.6%	-33.10 [-42.59 , -23.61]
Dinleyici 2015a	60.4	24.5	29	74.3	15.3	31	3.5%	-13.90 [-24.32 , -3.48]
Dinleyici 2015b	75.4	33.1	220	99.8	32.5	143	3.7%	-24.40 [-31.29 , -17.51]
El-Soud 2015	74.88	22.08	25	98.4	22.56	25	3.3%	-23.52 [-35.89 , -11.15]
Erdogan 2012	158.4	40.8	25	168	38.4	25	2.5%	-9.60 [-31.56 , 12.36]
Francavilla 2012	50.4	40.8	35	79.2	50.4	34	2.5%	-28.80 [-50.47 , -7.13]
Freedman 2015	71.1	78.3	61	63.5	64.3	62	2.2%	7.60 [-17.74 , 32.94]
Freedman 2018a	60.74	58.88	468	63.53	55.73	475	3.7%	-2.79 [-10.11 , 4.53]
Guarino 1997	76.8	34.61	52	141.6	33.26	48	3.3%	-64.80 [-78.10 , -51.50]
Huang 2014	43.2	38.4	82	69.6	33.6	77	3.4%	-26.40 [-37.60 , -15.20]
Isolauri 1994	36	16.8	21	55.2	19.2	21	3.5%	-19.20 [-30.11 , -8.29]
Kianifar 2009	81.6	108.6	32	108	105.2	30	0.9%	-26.40 [-79.63 , 26.83]
Kowalska-Duplaga 2004	54.6	30	86	61.6	34	87	3.6%	-7.00 [-16.55 , 2.55]
Kurugol 2005	112.8	60	100	132	76.8	100	2.8%	-19.20 [-38.30 , -0.10]
Lee 2001	74.4	16.8	50	86.4	19.2	50	3.7%	-12.00 [-19.07 , -4.93]
Mao 2008	67.2	40.2	70	67.2	40.5	71	3.3%	0.00 [-13.32 , 13.32]
Nixon 2012	67.7	36	63	74	39.5	66	3.3%	-6.30 [-19.33 , 6.73]
Pant 1996	45.6	14.4	14	79.2	55.2	12	1.8%	-33.60 [-65.73 , -1.47]
Park 2017	105.12	30.96	28	134.64	29.52	29	3.1%	-29.52 [-45.23 , -13.81]
Rosenfeldt 2002a	81.5	37.3	30	101.1	47.6	39	2.7%	-19.60 [-39.63 , 0.43]
Rosenfeldt 2002b	75.9	39.7	24	115.7	85	19	1.3%	-39.80 [-81.19 , 1.59]
Schnadower 2018	67.35	65.99	414	72.2	69.99	413	3.6%	-4.85 [-14.12 , 4.42]
Shornikova 1997b	36	26.4	21	60	36	25	2.8%	-24.00 [-42.07 , -5.93]
Shornikova 1997c	40.8	38.4	19	69.6	55.2	21	2.0%	-28.80 [-58.05 , 0.45]
Simadibrata 2013	58.74	38.54	38	83.37	49.83	38	2.7%	-24.63 [-44.66 , -4.60]
Szymanski 2006	83.6	55.6	46	96	71.5	41	2.1%	-12.40 [-39.55 , 14.75]
Szymanski 2019	58.7	43.8	44	66.9	57.4	47	2.6%	-8.20 [-29.10 , 12.70]
Villarruel 2007	112.8	46.56	35	147.84	76.8	37	2.0%	-35.04 [-64.20 , -5.88]
Vivatvakin 2006	38.4	16.8	36	69.6	40.8	35	3.2%	-31.20 [-45.79 , -16.61]
Xie 2013	132	38.4	50	139.2	40.8	50	3.1%	-7.20 [-22.73 , 8.33]
Subtotal (95% CI)			**2653**			**2572**	**100.0%**	**-19.18 [-24.98 , -13.39]**
Heterogeneity: Tau² = 221.86; Chi² = 337.56, df = 33 (P < 0.00001); I² = 90%								
Test for overall effect: Z = 6.49 (P < 0.00001)								
7.2.2 Child or adult mortality high								
Aggarwal 2014	60	13.3	100	78	13.3	100	5.5%	-18.00 [-21.69 , -14.31]
Basu 2007	163.3	25.68	323	158.4	28.16	323	5.5%	4.90 [0.74 , 9.06]
Basu 2009	122.9	27.8	186	173.5	30.5	185	5.4%	-50.60 [-56.54 , -44.66]
Bhat 2018	41.68	10.84	40	57.65	26.31	40	5.3%	-15.97 [-24.79 , -7.15]
Boudraa 2001	44.1	33.7	56	61.7	35.6	56	5.2%	-17.60 [-30.44 , -4.76]
Burande 2013	81.6	33.6	35	132	50.4	35	4.7%	-50.40 [-70.47 , -30.33]
Burki 2017	77.52	31.42	100	140.16	43.54	100	5.3%	-62.64 [-73.16 , -52.12]
Das 2016	60	11.85	30	89	20	28	5.4%	-29.00 [-37.54 , -20.46]
Dutta 2011	34	20.4	78	36.5	21.4	70	5.4%	-2.50 [-9.25 , 4.25]
Hamid 2019	76.8	31.2	160	79.2	26.4	150	5.4%	-2.40 [-8.82 , 4.02]
Henker 2007a	70.3	23.52	55	104.9	9.12	58	5.4%	-34.60 [-41.24 , -27.96]
Henker 2008	57.6	19.47	75	136.8	18.8	76	5.4%	-79.20 [-85.31 , -73.09]
Javeed 2018	104.9	33.1	157	110.2	36.1	157	5.4%	-5.30 [-12.96 , 2.36]
Narayanappa 2008	104.4	30.05	40	130.8	40.66	40	5.0%	-26.40 [-42.07 , -10.73]
Riaz 2012	49.55	23.72	43	66.34	29.27	47	5.3%	-16.79 [-27.76 , -5.82]
Sarkar 2005	90.4	45	115	94.2	43.3	115	5.2%	-3.80 [-15.21 , 7.61]
Shornikova 1997a	64.8	52.8	59	91.2	67.2	64	4.6%	-26.40 [-47.67 , -5.13]
Sudha 2019	75.25	12.96	59	81.6	15.43	60	5.5%	-6.35 [-11.47 , -1.23]
Teran 2009	57.1	25.4	25	74.6	26.6	25	5.1%	-17.50 [-31.92 , -3.08]
Subtotal (95% CI)			**1736**			**1729**	**100.0%**	**-24.05 [-35.28 , -12.83]**
Heterogeneity: Tau² = 593.05; Chi² = 803.03, df = 18 (P < 0.00001); I² = 98%								
Test for overall effect: Z = 4.20 (P < 0.0001)								



Analysis 7.2. (Continued)

Heterogeneity: Tau² = 593.05; Chi² = 803.03, df = 18 (P < 0.00001); I² = 98%
Test for overall effect: Z = 4.20 (P < 0.0001)



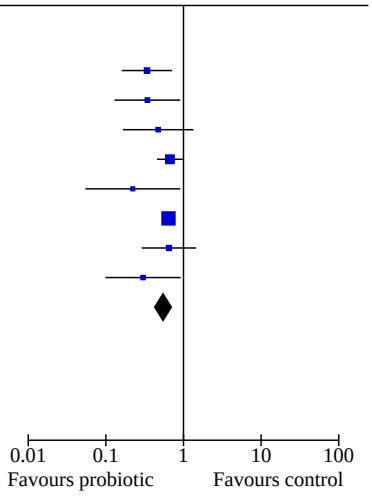
Comparison 8. Geographical region

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 Diarrhoea lasting ≥ 48 hours	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.1.1 Eur-A	8	500	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.43, 0.70]
8.2 Mean duration of diarrhoea	35		Mean Difference (IV, Random, 95% CI)	Subtotals only
8.2.1 Eur-A	8	601	Mean Difference (IV, Random, 95% CI)	-32.95 [-45.40, -20.50]
8.2.2 Eur-B	9	1271	Mean Difference (IV, Random, 95% CI)	-16.33 [-23.63, -9.03]
8.2.3 Sear-D	12	2402	Mean Difference (IV, Random, 95% CI)	-17.42 [-27.09, -7.75]
8.2.4 Wpr-B	6	850	Mean Difference (IV, Random, 95% CI)	-17.14 [-26.05, -8.23]

Analysis 8.1. Comparison 8: Geographical region, Outcome 1: Diarrhoea lasting ≥ 48 hours

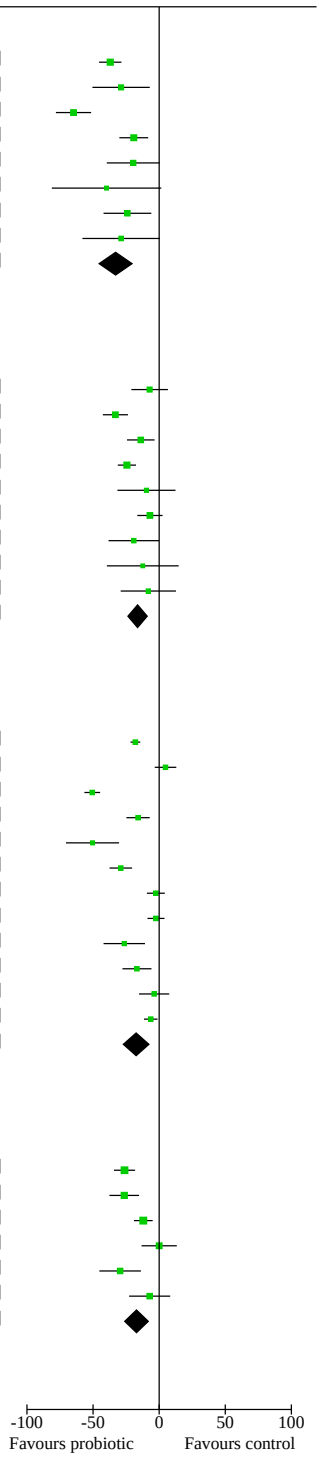
	Probiotic		Control			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
8.1.1 Eur-A							
Bruno 1981	6	25	17	24	9.1%	0.34 [0.16 , 0.71]	
D'Apuzzo 1982	4	21	10	18	5.7%	0.34 [0.13 , 0.91]	
Bruno 1983	3	10	7	11	5.0%	0.47 [0.17 , 1.34]	
Wunderlich 1989	19	40	27	38	23.0%	0.67 [0.46 , 0.98]	
Isolauri 1994	2	21	9	21	2.9%	0.22 [0.05 , 0.91]	
Buydens 1996	57	93	88	92	42.0%	0.64 [0.54 , 0.76]	
Shornikova 1997b	6	21	11	25	7.9%	0.65 [0.29 , 1.46]	
Shornikova 1997c	3	19	11	21	4.5%	0.30 [0.10 , 0.92]	
Subtotal (95% CI)		**250**		**250**	**100.0%**	**0.54 [0.43 , 0.70]**	
Total events:	100		180				

Heterogeneity: Tau² = 0.03; Chi² = 9.57, df = 7 (P = 0.21); I² = 27%
Test for overall effect: Z = 4.83 (P < 0.00001)



Analysis 8.2. Comparison 8: Geographical region, Outcome 2: Mean duration of diarrhoea

Study or Subgroup	Probiotic Mean	Probiotic SD	Probiotic Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
8.2.1 Eur-A								
Canani 2007	78.5	35.52	100	115.5	23.53	92	16.7%	-37.00 [-45.46 , -28.54]
Francavilla 2012	50.4	40.8	35	79.2	50.4	34	11.7%	-28.80 [-50.47 , -7.13]
Guarino 1997	76.8	34.61	52	141.6	33.26	48	15.0%	-64.80 [-78.10 , -51.50]
Isolauri 1994	36	16.8	21	55.2	19.2	21	15.9%	-19.20 [-30.11 , -8.29]
Rosenfeldt 2002a	81.5	37.3	30	101.1	47.6	39	12.3%	-19.60 [-39.63 , 0.43]
Rosenfeldt 2002b	75.9	39.7	24	115.7	85	19	6.0%	-39.80 [-81.19 , 1.59]
Shornikova 1997b	36	26.4	21	60	36	25	13.1%	-24.00 [-42.07 , -5.93]
Shornikova 1997c	40.8	38.4	19	69.6	55.2	21	9.1%	-28.80 [-58.05 , 0.45]
Subtotal (95% CI)			**302**			**299**	**100.0%**	**-32.95 [-45.40 , -20.50]**
Heterogeneity: Tau² = 222.32; Chi² = 31.70, df = 7 (P < 0.0001); I² = 78%								
Test for overall effect: Z = 5.19 (P < 0.00001)								
8.2.2 Eur-B								
Dalgic 2011	74.64	43.44	60	81.84	33.12	60	11.5%	-7.20 [-21.02 , 6.62]
Dinleyici 2014	70.7	26.1	64	103.8	28.4	63	14.8%	-33.10 [-42.59 , -23.61]
Dinleyici 2015a	60.4	24.5	29	74.3	15.3	31	14.0%	-13.90 [-24.32 , -3.48]
Dinleyici 2015b	75.4	33.1	220	99.8	32.5	143	16.7%	-24.40 [-31.29 , -17.51]
Erdogan 2012	158.4	40.8	25	168	38.4	25	7.1%	-9.60 [-31.56 , 12.36]
Kowalska-Duplaga 2004	54.6	30	86	61.6	34	87	14.7%	-7.00 [-16.55 , 2.55]
Kurugol 2005	112.8	60	100	132	76.8	100	8.4%	-19.20 [-38.30 , -0.10]
Szymanski 2006	83.6	55.6	46	96	71.5	41	5.3%	-12.40 [-39.55 , 14.75]
Szymanski 2019	58.7	43.8	44	66.9	57.4	47	7.5%	-8.20 [-29.10 , 12.70]
Subtotal (95% CI)			**674**			**597**	**100.0%**	**-16.33 [-23.63 , -9.03]**
Heterogeneity: Tau² = 70.60; Chi² = 22.55, df = 8 (P = 0.004); I² = 65%								
Test for overall effect: Z = 4.38 (P < 0.0001)								
8.2.3 Sear-D								
Aggarwal 2014	60	13.3	100	78	13.3	100	9.0%	-18.00 [-21.69 , -14.31]
Basu 2007	163.2	50.4	323	158.4	55.2	323	8.6%	4.80 [-3.35 , 12.95]
Basu 2009	122.9	27.8	186	173.5	30.5	185	8.8%	-50.60 [-56.54 , -44.66]
Bhat 2018	41.68	10.84	40	57.65	26.31	40	8.5%	-15.97 [-24.79 , -7.15]
Burande 2013	81.6	33.6	35	132	50.4	35	6.6%	-50.40 [-70.47 , -30.33]
Das 2016	60	11.85	30	89	20	28	8.5%	-29.00 [-37.54 , -20.46]
Dutta 2011	34	20.4	78	36.5	21.4	70	8.7%	-2.50 [-9.25 , 4.25]
Hamid 2019	76.8	31.2	160	79.2	26.4	150	8.8%	-2.40 [-8.82 , 4.02]
Narayanappa 2008	104.4	30.05	40	130.8	40.66	40	7.4%	-26.40 [-42.07 , -10.73]
Riaz 2012	49.55	23.72	43	66.34	29.27	47	8.2%	-16.79 [-27.76 , -5.82]
Sarkar 2005	90.4	45	115	94.2	43.3	115	8.1%	-3.80 [-15.21 , 7.61]
Sudha 2019	75.25	12.96	59	81.6	15.43	60	8.9%	-6.35 [-11.47 , -1.23]
Subtotal (95% CI)			**1209**			**1193**	**100.0%**	**-17.42 [-27.09 , -7.75]**
Heterogeneity: Tau² = 266.90; Chi² = 229.02, df = 11 (P < 0.00001); I² = 95%								
Test for overall effect: Z = 3.53 (P = 0.0004)								
8.2.4 Wpr-B								
Chen 2010	60.1	31.7	150	86.3	37.6	143	19.8%	-26.20 [-34.18 , -18.22]
Huang 2014	43.2	38.4	82	69.6	33.6	77	17.1%	-26.40 [-37.60 , -15.20]
Lee 2001	74.4	16.8	50	86.4	19.2	50	20.5%	-12.00 [-19.07 , -4.93]
Mao 2008	67.2	40.2	70	67.2	40.5	71	15.4%	0.00 [-13.32 , 13.32]
Park 2017	105.12	30.96	28	134.64	29.52	29	13.6%	-29.52 [-45.23 , -13.81]
Xie 2013	132	38.4	50	139.2	40.8	50	13.7%	-7.20 [-22.73 , 8.33]
Subtotal (95% CI)			**430**			**420**	**100.0%**	**-17.14 [-26.05 , -8.23]**
Heterogeneity: Tau² = 88.00; Chi² = 19.88, df = 5 (P = 0.001); I² = 75%								
Test for overall effect: Z = 3.77 (P = 0.0002)								



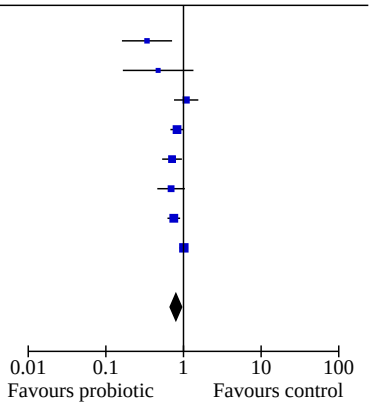
Comparison 9. Exposure to antibiotics

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.1 Diarrhoea lasting ≥ 48 hours	8	1717	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.67, 0.95]
9.2 Duration of diarrhoea	6	1674	Mean Difference (IV, Random, 95% CI)	-18.94 [-37.35, -0.52]

Analysis 9.1. Comparison 9: Exposure to antibiotics, Outcome 1: Diarrhoea lasting ≥ 48 hours

Study or Subgroup	Probiotic Events	Probiotic Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Bruno 1981	6	25	17	24	4.3%	0.34 [0.16 , 0.71]
Bruno 1983	3	10	7	11	2.4%	0.47 [0.17 , 1.34]
Bhatnagar 1998	27	47	26	49	11.6%	1.08 [0.76 , 1.55]
Guandalini 2000	78	147	90	140	18.1%	0.83 [0.68 , 1.00]
Costa-Ribeiro 2003	31	61	45	63	14.0%	0.71 [0.53 , 0.95]
Henker 2007a	21	55	32	58	10.1%	0.69 [0.46 , 1.04]
Burki 2017	60	100	80	100	18.4%	0.75 [0.62 , 0.90]
Freedman 2018a	228	414	225	413	21.1%	1.01 [0.89 , 1.14]
Total (95% CI)		**859**		**858**	**100.0%**	**0.80 [0.67 , 0.95]**
Total events:	454		522			

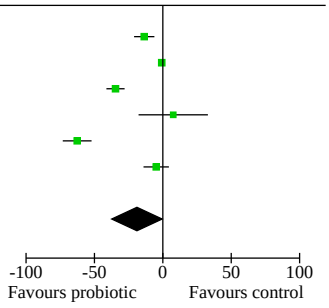
Heterogeneity: Tau² = 0.03; Chi² = 20.26, df = 7 (P = 0.005); I² = 65%
Test for overall effect: Z = 2.59 (P = 0.010)
Test for subgroup differences: Not applicable



Analysis 9.2. Comparison 9: Exposure to antibiotics, Outcome 2: Duration of diarrhoea

Study or Subgroup	Probiotic Mean	Probiotic SD	Probiotic Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Guandalini 2000	58.3	27.6	147	71.9	35.8	140	17.4%	-13.60 [-21.02 , -6.18]
Costa-Ribeiro 2003	38.3	3.78	61	39.1	4.6	63	17.8%	-0.80 [-2.28 , 0.68]
Henker 2007a	70.3	23.52	55	104.9	9.12	58	17.5%	-34.60 [-41.24 , -27.96]
Freedman 2015	71.1	78.3	61	63.5	64.3	62	13.4%	7.60 [-17.74 , 32.94]
Burki 2017	77.52	31.42	100	140.16	43.54	100	16.9%	-62.64 [-73.16 , -52.12]
Freedman 2018a	67.35	65.99	414	72.2	69.99	413	17.1%	-4.85 [-14.12 , 4.42]
Total (95% CI)			**838**			**836**	**100.0%**	**-18.94 [-37.35 , -0.52]**

Heterogeneity: Tau² = 494.26; Chi² = 225.94, df = 5 (P < 0.00001); I² = 98%
Test for overall effect: Z = 2.01 (P = 0.04)
Test for subgroup differences: Not applicable



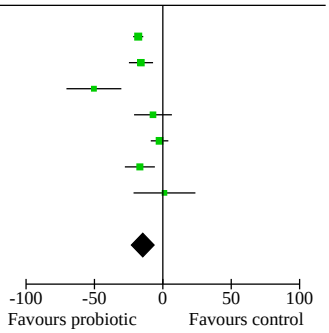
Comparison 10. Use of zinc

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.1 Duration of diarrhoea	7	934	Mean Difference (IV, Random, 95% CI)	-14.68 [-22.94, -6.42]

Analysis 10.1. Comparison 10: Use of zinc, Outcome 1: Duration of diarrhoea

Study or Subgroup	Probiotic Mean	Probiotic SD	Probiotic Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Aggarwal 2014	60	13.3	100	78	13.3	100	19.7%	-18.00 [-21.69 , -14.31]
Bhat 2018	41.68	10.84	40	57.65	26.31	40	16.6%	-15.97 [-24.79 , -7.15]
Burande 2013	81.6	33.6	35	132	50.4	35	9.3%	-50.40 [-70.47 , -30.33]
Dalgic 2011	74.64	43.44	60	81.84	33.12	60	13.0%	-7.20 [-21.02 , 6.62]
Hamid 2019	76.8	31.2	160	79.2	26.4	150	18.2%	-2.40 [-8.82 , 4.02]
Riaz 2012	49.55	23.72	43	66.34	29.27	47	15.1%	-16.79 [-27.76 , -5.82]
Ritchie 2010	52.4	49.8	33	51.2	42.4	31	8.1%	1.20 [-21.42 , 23.82]
Total (95% CI)			**471**			**463**	**100.0%**	**-14.68 [-22.94 , -6.42]**

Heterogeneity: Tau² = 86.58; Chi² = 32.58, df = 6 (P < 0.0001); I² = 82%
Test for overall effect: Z = 3.48 (P = 0.0005)
Test for subgroup differences: Not applicable

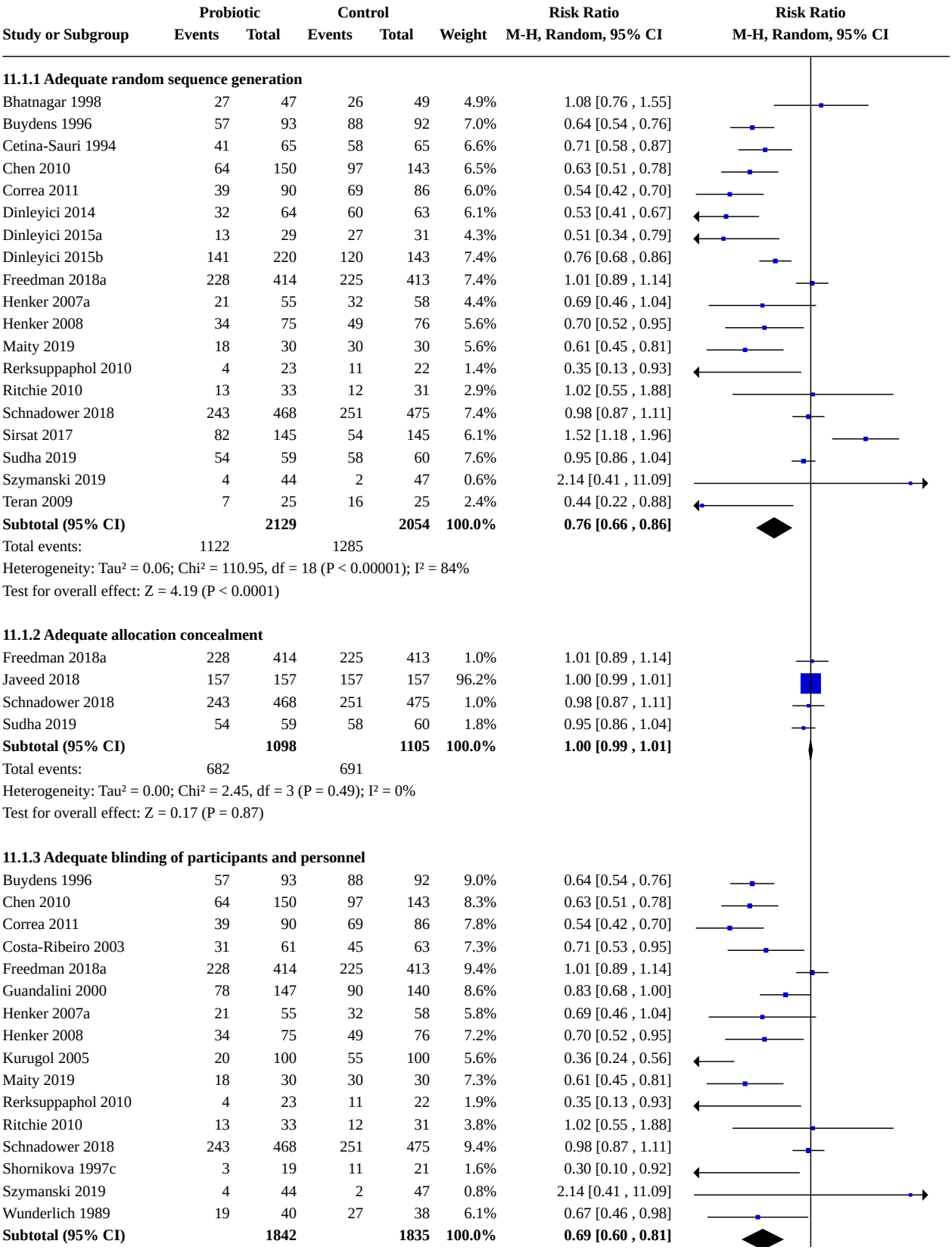


Comparison 11. Risk of bias

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.1 Diarrhoea lasting ≥ 48 hours	36		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
11.1.1 Adequate random sequence generation	19	4183	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.66, 0.86]
11.1.2 Adequate allocation concealment	4	2203	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.99, 1.01]
11.1.3 Adequate blinding of participants and personnel	16	3677	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.60, 0.81]
11.1.4 Adequate blinding of outcome assessment	16	3941	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.65, 0.83]
11.1.5 Adequate participant follow-up	25	4622	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.50, 0.80]
11.1.6 Adequate outcome reporting	33	5803	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.53, 0.81]
11.1.7 Low risk of bias for all parameters	2	1770	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.91, 1.09]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.2 Mean duration of diarrhoea	56		Mean Difference (IV, Random, 95% CI)	Subtotals only
11.2.1 Adequate random sequence generation	28	5949	Mean Difference (IV, Random, 95% CI)	-22.20 [-30.88, -13.51]
11.2.2 Adequate allocation concealment	10	3599	Mean Difference (IV, Random, 95% CI)	-11.77 [-24.11, 0.57]
11.2.3 Adequate blinding of participants and personnel	22	4956	Mean Difference (IV, Random, 95% CI)	-18.78 [-30.37, -7.18]
11.2.4 Adequate blinding of outcome assessment	24	5630	Mean Difference (IV, Random, 95% CI)	-21.43 [-31.85, -11.02]
11.2.5 Adequate participant follow-up	43	7785	Mean Difference (IV, Random, 95% CI)	-20.93 [-27.24, -14.62]
11.2.6 Adequate outcome reporting	53	8861	Mean Difference (IV, Random, 95% CI)	-21.60 [-27.39, -15.81]
11.2.7 Low risk of bias for all parameters	6	3058	Mean Difference (IV, Random, 95% CI)	-8.64 [-29.38, 12.10]

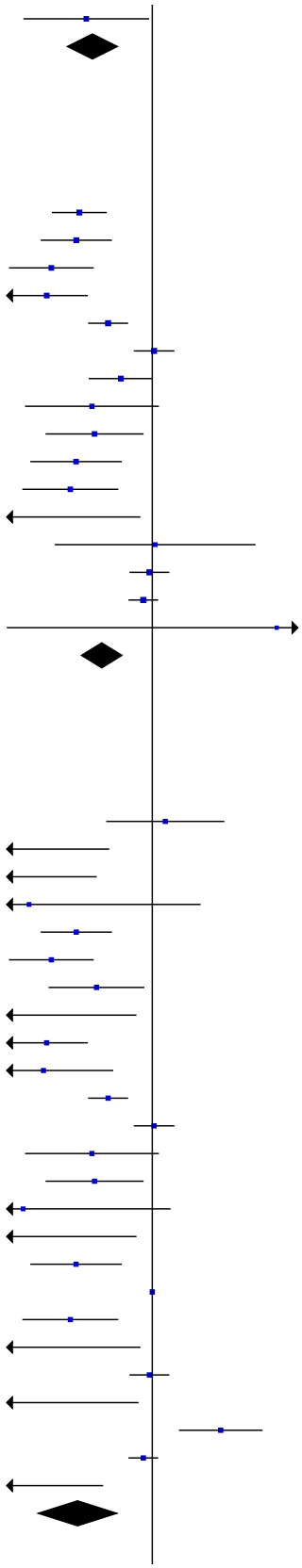
Analysis 11.1. Comparison 11: Risk of bias, Outcome 1: Diarrhoea lasting ≥ 48 hours



Study or Subgroup	Probiotic Events	Probiotic Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
11.1.1 Adequate random sequence generation						
Bhatnagar 1998	27	47	26	49	4.9%	1.08 [0.76 , 1.55]
Buydens 1996	57	93	88	92	7.0%	0.64 [0.54 , 0.76]
Cetina-Sauri 1994	41	65	58	65	6.6%	0.71 [0.58 , 0.87]
Chen 2010	64	150	97	143	6.5%	0.63 [0.51 , 0.78]
Correa 2011	39	90	69	86	6.0%	0.54 [0.42 , 0.70]
Dinleyici 2014	32	64	60	63	6.1%	0.53 [0.41 , 0.67]
Dinleyici 2015a	13	29	27	31	4.3%	0.51 [0.34 , 0.79]
Dinleyici 2015b	141	220	120	143	7.4%	0.76 [0.68 , 0.86]
Freedman 2018a	228	414	225	413	7.4%	1.01 [0.89 , 1.14]
Henker 2007a	21	55	32	58	4.4%	0.69 [0.46 , 1.04]
Henker 2008	34	75	49	76	5.6%	0.70 [0.52 , 0.95]
Maity 2019	18	30	30	30	5.6%	0.61 [0.45 , 0.81]
Rerksuppaphol 2010	4	23	11	22	1.4%	0.35 [0.13 , 0.93]
Ritchie 2010	13	33	12	31	2.9%	1.02 [0.55 , 1.88]
Schnadower 2018	243	468	251	475	7.4%	0.98 [0.87 , 1.11]
Sirsat 2017	82	145	54	145	6.1%	1.52 [1.18 , 1.96]
Sudha 2019	54	59	58	60	7.6%	0.95 [0.86 , 1.04]
Szymanski 2019	4	44	2	47	0.6%	2.14 [0.41 , 11.09]
Teran 2009	7	25	16	25	2.4%	0.44 [0.22 , 0.88]
Subtotal (95% CI)		**2129**		**2054**	**100.0%**	**0.76 [0.66 , 0.86]**
Total events:	1122		1285			
Heterogeneity: Tau² = 0.06; Chi² = 110.95, df = 18 (P < 0.00001); I² = 84%						
Test for overall effect: Z = 4.19 (P < 0.0001)						
11.1.2 Adequate allocation concealment						
Freedman 2018a	228	414	225	413	1.0%	1.01 [0.89 , 1.14]
Javeed 2018	157	157	157	157	96.2%	1.00 [0.99 , 1.01]
Schnadower 2018	243	468	251	475	1.0%	0.98 [0.87 , 1.11]
Sudha 2019	54	59	58	60	1.8%	0.95 [0.86 , 1.04]
Subtotal (95% CI)		**1098**		**1105**	**100.0%**	**1.00 [0.99 , 1.01]**
Total events:	682		691			
Heterogeneity: Tau² = 0.00; Chi² = 2.45, df = 3 (P = 0.49); I² = 0%						
Test for overall effect: Z = 0.17 (P = 0.87)						
11.1.3 Adequate blinding of participants and personnel						
Buydens 1996	57	93	88	92	9.0%	0.64 [0.54 , 0.76]
Chen 2010	64	150	97	143	8.3%	0.63 [0.51 , 0.78]
Correa 2011	39	90	69	86	7.8%	0.54 [0.42 , 0.70]
Costa-Ribeiro 2003	31	61	45	63	7.3%	0.71 [0.53 , 0.95]
Freedman 2018a	228	414	225	413	9.4%	1.01 [0.89 , 1.14]
Guandalini 2000	78	147	90	140	8.6%	0.83 [0.68 , 1.00]
Henker 2007a	21	55	32	58	5.8%	0.69 [0.46 , 1.04]
Henker 2008	34	75	49	76	7.2%	0.70 [0.52 , 0.95]
Kurugol 2005	20	100	55	100	5.6%	0.36 [0.24 , 0.56]
Maity 2019	18	30	30	30	7.3%	0.61 [0.45 , 0.81]
Rerksuppaphol 2010	4	23	11	22	1.9%	0.35 [0.13 , 0.93]
Ritchie 2010	13	33	12	31	3.8%	1.02 [0.55 , 1.88]
Schnadower 2018	243	468	251	475	9.4%	0.98 [0.87 , 1.11]
Shornikova 1997c	3	19	11	21	1.6%	0.30 [0.10 , 0.92]
Szymanski 2019	4	44	2	47	0.8%	2.14 [0.41 , 11.09]
Wunderlich 1989	19	40	27	38	6.1%	0.67 [0.46 , 0.98]
Subtotal (95% CI)		**1842**		**1835**	**100.0%**	**0.69 [0.60 , 0.81]**

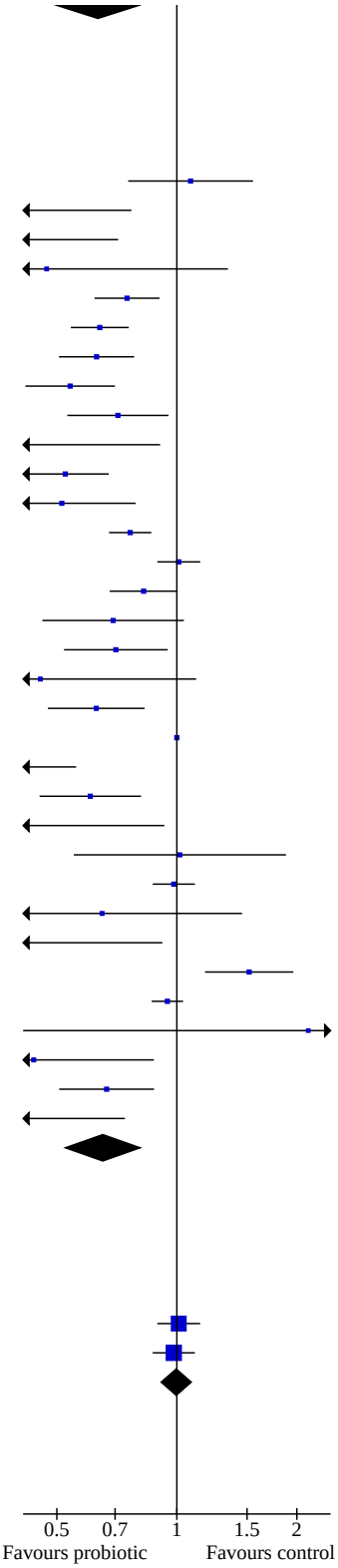
Analysis 11.1. (Continued)

Wunderlich 1989	19	40	27	38	6.1%	0.67 [0.46 , 0.98]
Subtotal (95% CI)		**1842**		**1835**	**100.0%**	**0.69 [0.60 , 0.81]**
Total events:	876		1094			
Heterogeneity: Tau² = 0.06; Chi² = 71.71, df = 15 (P < 0.00001); I² = 79%						
Test for overall effect: Z = 4.71 (P < 0.00001)						
11.1.4 Adequate blinding of outcome assessment						
Buydens 1996	57	93	88	92	8.1%	0.64 [0.54 , 0.76]
Chen 2010	64	150	97	143	7.4%	0.63 [0.51 , 0.78]
Correa 2011	39	90	69	86	6.7%	0.54 [0.42 , 0.70]
Dinleyici 2014	32	64	60	63	6.8%	0.53 [0.41 , 0.67]
Dinleyici 2015b	141	220	120	143	8.7%	0.76 [0.68 , 0.86]
Freedman 2018a	228	414	225	413	8.7%	1.01 [0.89 , 1.14]
Guandalini 2000	78	147	90	140	7.7%	0.83 [0.68 , 1.00]
Henker 2007a	21	55	32	58	4.7%	0.69 [0.46 , 1.04]
Henker 2008	34	75	49	76	6.1%	0.70 [0.52 , 0.95]
Jasinski 2002	25	45	46	52	6.4%	0.63 [0.48 , 0.83]
Maity 2019	18	30	30	30	6.2%	0.61 [0.45 , 0.81]
Rerksuppaphol 2010	4	23	11	22	1.3%	0.35 [0.13 , 0.93]
Ritchie 2010	13	33	12	31	2.8%	1.02 [0.55 , 1.88]
Schnadower 2018	243	468	251	475	8.7%	0.98 [0.87 , 1.11]
Sudha 2019	54	59	58	60	9.1%	0.95 [0.86 , 1.04]
Szymanski 2019	4	44	2	47	0.5%	2.14 [0.41 , 11.09]
Subtotal (95% CI)		**2010**		**1931**	**100.0%**	**0.73 [0.65 , 0.83]**
Total events:	1055		1240			
Heterogeneity: Tau² = 0.04; Chi² = 81.04, df = 15 (P < 0.00001); I² = 81%						
Test for overall effect: Z = 4.91 (P < 0.00001)						
11.1.5 Adequate participant follow-up						
Bhatnagar 1998	27	47	26	49	4.5%	1.08 [0.76 , 1.55]
Boudraa 2001	9	56	23	56	3.6%	0.39 [0.20 , 0.77]
Bruno 1981	6	25	17	24	3.4%	0.34 [0.16 , 0.71]
Bruno 1983	3	10	7	11	2.6%	0.47 [0.17 , 1.34]
Chen 2010	64	150	97	143	4.8%	0.63 [0.51 , 0.78]
Correa 2011	39	90	69	86	4.8%	0.54 [0.42 , 0.70]
Costa-Ribeiro 2003	31	61	45	63	4.7%	0.71 [0.53 , 0.95]
D'Apuzzo 1982	4	21	10	18	2.7%	0.34 [0.13 , 0.91]
Dinleyici 2014	32	64	60	63	4.8%	0.53 [0.41 , 0.67]
Dinleyici 2015a	13	29	27	31	4.3%	0.51 [0.34 , 0.79]
Dinleyici 2015b	141	220	120	143	5.0%	0.76 [0.68 , 0.86]
Freedman 2018a	228	414	225	413	5.0%	1.01 [0.89 , 1.14]
Henker 2007a	21	55	32	58	4.4%	0.69 [0.46 , 1.04]
Henker 2008	34	75	49	76	4.7%	0.70 [0.52 , 0.95]
Hernandez 1998	5	25	11	25	2.9%	0.45 [0.18 , 1.12]
Isolauri 1994	2	21	9	21	1.8%	0.22 [0.05 , 0.91]
Jasinski 2002	25	45	46	52	4.7%	0.63 [0.48 , 0.83]
Javeed 2018	157	157	157	157	5.0%	1.00 [0.99 , 1.01]
Maity 2019	18	30	30	30	4.7%	0.61 [0.45 , 0.81]
Rerksuppaphol 2010	4	23	11	22	2.7%	0.35 [0.13 , 0.93]
Schnadower 2018	243	468	251	475	5.0%	0.98 [0.87 , 1.11]
Shornikova 1997c	3	19	11	21	2.4%	0.30 [0.10 , 0.92]
Sirsat 2017	82	145	54	145	4.8%	1.52 [1.18 , 1.96]
Sudha 2019	54	59	58	60	5.0%	0.95 [0.86 , 1.04]
Vivatvakin 2006	2	36	11	35	1.8%	0.18 [0.04 , 0.74]
Subtotal (95% CI)		**2345**		**2277**	**100.0%**	**0.63 [0.50 , 0.80]**
Total events:	1247		1456			
Heterogeneity: Tau² = 0.29; Chi² = 1037.63, df = 24 (P < 0.00001); I² = 98%						



Analysis 11.1. (Continued)

Total events:	1247		1456			
Heterogeneity: Tau² = 0.29; Chi² = 1037.63, df = 24 (P < 0.00001); I² = 98%						
Test for overall effect: Z = 3.74 (P = 0.0002)						
11.1.6 Adequate outcome reporting						
Bhatnagar 1998	27	47	26	49	3.4%	1.08 [0.76 , 1.55]
Boudraa 2001	9	56	23	56	2.7%	0.39 [0.20 , 0.77]
Bruno 1981	6	25	17	24	2.6%	0.34 [0.16 , 0.71]
Bruno 1983	3	10	7	11	2.0%	0.47 [0.17 , 1.34]
Burki 2017	60	100	80	100	3.6%	0.75 [0.62 , 0.90]
Buydens 1996	57	93	88	92	3.6%	0.64 [0.54 , 0.76]
Chen 2010	64	150	97	143	3.6%	0.63 [0.51 , 0.78]
Correa 2011	39	90	69	86	3.5%	0.54 [0.42 , 0.70]
Costa-Ribeiro 2003	31	61	45	63	3.5%	0.71 [0.53 , 0.95]
D'Apuzzo 1982	4	21	10	18	2.1%	0.34 [0.13 , 0.91]
Dinleyici 2014	32	64	60	63	3.5%	0.53 [0.41 , 0.67]
Dinleyici 2015a	13	29	27	31	3.2%	0.51 [0.34 , 0.79]
Dinleyici 2015b	141	220	120	143	3.7%	0.76 [0.68 , 0.86]
Freedman 2018a	228	414	225	413	3.7%	1.01 [0.89 , 1.14]
Guandalini 2000	78	147	90	140	3.6%	0.83 [0.68 , 1.00]
Henker 2007a	21	55	32	58	3.3%	0.69 [0.46 , 1.04]
Henker 2008	34	75	49	76	3.5%	0.70 [0.52 , 0.95]
Hernandez 1998	5	25	11	25	2.3%	0.45 [0.18 , 1.12]
Jasinski 2002	25	45	46	52	3.5%	0.63 [0.48 , 0.83]
Javeed 2018	157	157	157	157	3.7%	1.00 [0.99 , 1.01]
Kurugol 2005	20	100	55	100	3.2%	0.36 [0.24 , 0.56]
Maity 2019	18	30	30	30	3.5%	0.61 [0.45 , 0.81]
Rerksuppaphol 2010	4	23	11	22	2.1%	0.35 [0.13 , 0.93]
Ritchie 2010	13	33	12	31	2.9%	1.02 [0.55 , 1.88]
Schnadower 2018	243	468	251	475	3.7%	0.98 [0.87 , 1.11]
Shornikova 1997b	6	21	11	25	2.4%	0.65 [0.29 , 1.46]
Shornikova 1997c	3	19	11	21	1.9%	0.30 [0.10 , 0.92]
Sirsat 2017	82	145	54	145	3.5%	1.52 [1.18 , 1.96]
Sudha 2019	54	59	58	60	3.7%	0.95 [0.86 , 1.04]
Szymanski 2019	4	44	2	47	1.2%	2.14 [0.41 , 11.09]
Teran 2009	7	25	16	25	2.7%	0.44 [0.22 , 0.88]
Urganci 2001	28	50	42	50	3.5%	0.67 [0.51 , 0.88]
Vivatvakin 2006	2	36	11	35	1.4%	0.18 [0.04 , 0.74]
Subtotal (95% CI)		**2937**		**2866**	**100.0%**	**0.65 [0.53 , 0.81]**
Total events:	1518		1843			
Heterogeneity: Tau² = 0.33; Chi² = 1422.42, df = 32 (P < 0.00001); I² = 98%						
Test for overall effect: Z = 3.89 (P = 0.0001)						
11.1.7 Low risk of bias for all parameters						
Freedman 2018a	228	414	225	413	49.1%	1.01 [0.89 , 1.14]
Schnadower 2018	243	468	251	475	50.9%	0.98 [0.87 , 1.11]
Subtotal (95% CI)		**882**		**888**	**100.0%**	**1.00 [0.91 , 1.09]**
Total events:	471		476			
Heterogeneity: Tau² = 0.00; Chi² = 0.10, df = 1 (P = 0.75); I² = 0%						
Test for overall effect: Z = 0.08 (P = 0.94)						



Analysis 11.2. Comparison 11: Risk of bias, Outcome 2: Mean duration of diarrhoea

Study or Subgroup	Probiotic Mean	Probiotic SD	Probiotic Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
11.2.1 Adequate random sequence generation								
Aggarwal 2014	60	13.3	100	78	13.3	100	4.0%	-18.00 [-21.69 , -14.31]
Basu 2007	163.2	50.4	323	158.4	55.2	323	3.9%	4.80 [-3.35 , 12.95]
Basu 2009	122.9	27.8	186	173.5	30.5	185	3.9%	-50.60 [-56.54 , -44.66]
Burande 2013	81.6	33.6	35	132	50.4	35	3.3%	-50.40 [-70.47 , -30.33]
Canani 2007	78.5	35.52	100	115.5	23.53	92	3.9%	-37.00 [-45.46 , -28.54]
Chen 2010	60.1	31.7	150	86.3	37.6	143	3.9%	-26.20 [-34.18 , -18.22]
Dinleyici 2014	70.7	26.1	64	103.8	28.4	63	3.8%	-33.10 [-42.59 , -23.61]
Dinleyici 2015a	60.4	24.5	29	74.3	15.3	31	3.8%	-13.90 [-24.32 , -3.48]
Dinleyici 2015b	75.4	33.1	220	99.8	32.5	143	3.9%	-24.40 [-31.29 , -17.51]
Dutta 2011	34	20.4	78	36.5	21.4	70	3.9%	-2.50 [-9.25 , 4.25]
Francavilla 2012	50.4	40.8	35	79.2	50.4	34	3.2%	-28.80 [-50.47 , -7.13]
Freedman 2015	71.1	78.3	61	63.5	64.3	62	3.0%	7.60 [-17.74 , 32.94]
Freedman 2018a	67.35	65.99	414	72.2	69.99	413	3.8%	-4.85 [-14.12 , 4.42]
Guarino 1997	76.8	34.61	52	141.6	33.26	48	3.7%	-64.80 [-78.10 , -51.50]
Henker 2007a	70.3	23.52	55	104.9	9.12	58	3.9%	-34.60 [-41.24 , -27.96]
Henker 2008	57.6	19.47	75	136.8	18.8	76	3.9%	-79.20 [-85.31 , -73.09]
Huang 2014	43.2	38.4	82	69.6	33.6	77	3.8%	-26.40 [-37.60 , -15.20]
Kianifar 2009	81.6	108.6	32	108	105.2	30	1.6%	-26.40 [-79.63 , 26.83]
Nixon 2012	67.7	36	63	74	39.5	66	3.7%	-6.30 [-19.33 , 6.73]
Riaz 2012	49.55	23.72	43	66.34	29.27	47	3.8%	-16.79 [-27.76 , -5.82]
Ritchie 2010	52.4	49.8	33	51.2	42.4	31	3.2%	1.20 [-21.42 , 23.82]
Sarkar 2005	90.4	45	115	94.2	43.3	115	3.8%	-3.80 [-15.21 , 7.61]
Schnadower 2018	60.74	58.88	468	63.53	55.73	475	3.9%	-2.79 [-10.11 , 4.53]
Sudha 2019	75.25	12.96	59	81.6	15.43	60	4.0%	-6.35 [-11.47 , -1.23]
Szymanski 2006	83.6	55.6	46	96	71.5	41	2.9%	-12.40 [-39.55 , 14.75]
Szymanski 2019	58.7	43.8	44	66.9	57.4	47	3.3%	-8.20 [-29.10 , 12.70]
Teran 2009	57.1	25.4	25	74.6	26.6	25	3.6%	-17.50 [-31.92 , -3.08]
Villarruel 2007	112.8	46.56	35	147.8	76.8	37	2.8%	-35.00 [-64.16 , -5.84]
Subtotal (95% CI)			**3022**			**2927**	**100.0%**	**-22.20 [-30.88 , -13.51]**
Heterogeneity: Tau² = 489.35; Chi² = 687.51, df = 27 (P < 0.00001); I² = 96%								
Test for overall effect: Z = 5.01 (P < 0.00001)								
11.2.2 Adequate allocation concealment								
Basu 2007	163.2	50.4	323	158.4	55.2	323	10.3%	4.80 [-3.35 , 12.95]
Basu 2009	122.9	27.8	186	173.5	30.5	185	10.5%	-50.60 [-56.54 , -44.66]
Das 2016	60	11.85	30	89	20	28	10.2%	-29.00 [-37.54 , -20.46]
Dutta 2011	34	20.4	78	36.5	21.4	70	10.4%	-2.50 [-9.25 , 4.25]
El-Soud 2015	74.88	22.08	25	98.4	22.56	25	9.7%	-23.52 [-35.89 , -11.15]
Freedman 2015	71.1	78.3	61	63.5	64.3	62	7.4%	7.60 [-17.74 , 32.94]
Freedman 2018a	67.35	65.99	414	72.2	69.99	413	10.1%	-4.85 [-14.12 , 4.42]
Javeed 2018	104.9	33.1	157	110.2	36.1	157	10.3%	-5.30 [-12.96 , 2.36]
Schnadower 2018	60.74	58.88	468	63.53	55.73	475	10.4%	-2.79 [-10.11 , 4.53]
Sudha 2019	75.25	12.96	59	81.6	15.43	60	10.6%	-6.35 [-11.47 , -1.23]
Subtotal (95% CI)			**1801**			**1798**	**100.0%**	**-11.77 [-24.11 , 0.57]**
Heterogeneity: Tau² = 368.22; Chi² = 220.65, df = 9 (P < 0.00001); I² = 96%								
Test for overall effect: Z = 1.87 (P = 0.06)								
11.2.3 Adequate blinding of participants and personnel								
Basu 2007	163.2	50.4	323	158.4	55.2	323	5.0%	4.80 [-3.35 , 12.95]
Basu 2009	122.9	27.8	186	173.5	30.5	185	5.1%	-50.60 [-56.54 , -44.66]
Chen 2010	60.1	31.7	150	86.3	37.6	143	5.0%	-26.20 [-34.18 , -18.22]
Costa-Ribeiro 2003	38.3	3.78	61	39.1	4.6	63	5.1%	-0.80 [-2.28 , 0.68]
Dutta 2011	34	20.4	78	36.5	21.4	70	5.1%	-2.50 [-9.25 , 4.25]
Francavilla 2012	50.4	40.8	35	79.2	50.4	34	4.4%	-28.80 [-50.47 , -7.13]
Freedman 2015	71.1	78.3	61	63.5	64.3	62	4.1%	7.60 [-17.74 , 32.94]
Freedman 2018a	67.35	65.99	414	72.2	69.99	413	5.0%	-4.85 [-14.12 , 4.42]
Guandalini 2000	58.3	27.6	147	71.9	35.8	140	5.0%	-13.60 [-21.02 , -6.18]
Henker 2007a	70.3	23.52	55	104.9	9.12	58	5.1%	-34.60 [-41.24 , -27.96]
Henker 2008	57.6	19.47	75	136.8	18.8	76	5.1%	-79.20 [-85.31 , -73.09]
Kianifar 2009	81.6	108.6	32	108	105.2	30	2.5%	-26.40 [-79.63 , 26.83]
Kurugol 2005	112.8	60	100	132	76.8	100	4.5%	-19.20 [-38.30 , -0.10]

Analysis 11.2. (Continued)

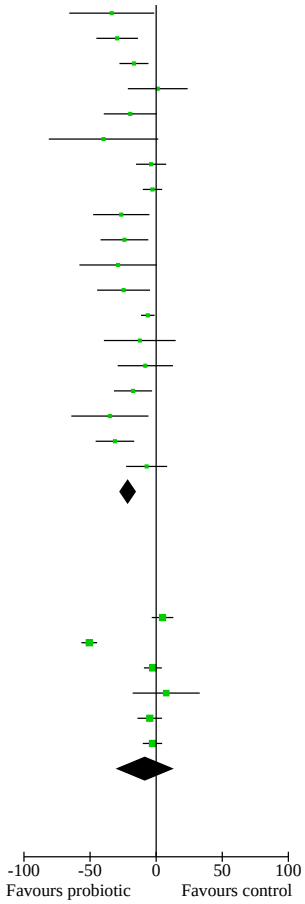
Kianifar 2009	81.6	108.6	32	108	105.2	30	2.5%	-26.40 [-79.63 , 26.83]
Kurugol 2005	112.8	60	100	132	76.8	100	4.5%	-19.20 [-38.30 , -0.10]
Nixon 2012	67.7	36	63	74	39.5	66	4.8%	-6.30 [-19.33 , 6.73]
Pant 1996	45.6	14.4	14	79.2	55.2	12	3.7%	-33.60 [-65.73 , -1.47]
Riaz 2012	49.55	23.72	43	66.34	29.27	47	4.9%	-16.79 [-27.76 , -5.82]
Ritchie 2010	52.4	49.8	33	51.2	42.4	31	4.3%	1.20 [-21.42 , 23.82]
Schnadower 2018	60.74	58.88	468	63.53	55.73	475	5.0%	-2.79 [-10.11 , 4.53]
Shornikova 1997c	40.8	38.4	19	69.6	55.2	21	3.9%	-28.80 [-58.05 , 0.45]
Szymanski 2006	83.6	55.6	46	96	71.5	41	4.0%	-12.40 [-39.55 , 14.75]
Szymanski 2019	58.7	43.8	44	66.9	57.4	47	4.4%	-8.20 [-29.10 , 12.70]
Villarruel 2007	112.8	46.56	35	147.8	76.8	37	3.9%	-35.00 [-64.16 , -5.84]
Subtotal (95% CI)			**2482**			**2474**	**100.0%**	**-18.78 [-30.37 , -7.18]**
Heterogeneity: Tau² = 679.66; Chi² = 924.93, df = 21 (P < 0.00001); I² = 98%								
Test for overall effect: Z = 3.17 (P = 0.002)								
11.2.4 Adequate blinding of outcome assessment								
Basu 2007	163.2	50.4	323	158.4	55.2	323	4.6%	4.80 [-3.35 , 12.95]
Basu 2009	122.9	27.8	186	173.5	30.5	185	4.6%	-50.60 [-56.54 , -44.66]
Canani 2007	78.5	35.52	100	115.5	23.53	92	4.5%	-37.00 [-45.46 , -28.54]
Chen 2010	60.1	31.7	150	86.3	37.6	143	4.6%	-26.20 [-34.18 , -18.22]
Dinleyici 2014	70.7	26.1	64	103.8	28.4	63	4.5%	-33.10 [-42.59 , -23.61]
Dinleyici 2015b	75.4	33.1	220	99.8	32.5	143	4.6%	-24.40 [-31.29 , -17.51]
Dutta 2011	34	20.4	78	36.5	21.4	70	4.6%	-2.50 [-9.25 , 4.25]
Francavilla 2012	50.4	40.8	35	79.2	50.4	34	3.9%	-28.80 [-50.47 , -7.13]
Freedman 2015	71.1	78.3	61	63.5	64.3	62	3.7%	7.60 [-17.74 , 32.94]
Freedman 2018a	67.35	65.99	414	72.2	69.99	413	4.5%	-4.85 [-14.12 , 4.42]
Guandalini 2000	58.3	27.6	147	71.9	35.8	140	4.6%	-13.60 [-21.02 , -6.18]
Henker 2007a	70.3	23.52	55	104.9	9.12	58	4.6%	-34.60 [-41.24 , -27.96]
Henker 2008	57.6	19.47	75	136.8	18.8	76	4.6%	-79.20 [-85.31 , -73.09]
Jasinski 2002	74.6	47.76	45	133.4	53.76	52	4.0%	-58.80 [-79.00 , -38.60]
Kianifar 2009	81.6	108.6	32	108	105.2	30	2.1%	-26.40 [-79.63 , 26.83]
Nixon 2012	67.7	36	63	74	39.5	66	4.4%	-6.30 [-19.33 , 6.73]
Pant 1996	45.6	14.4	14	79.2	55.2	12	3.2%	-33.60 [-65.73 , -1.47]
Ritchie 2010	52.4	49.8	33	51.2	42.4	31	3.8%	1.20 [-21.42 , 23.82]
Sarkar 2005	90.4	45	115	94.2	43.3	115	4.4%	-3.80 [-15.21 , 7.61]
Schnadower 2018	60.74	58.88	468	63.53	55.73	475	4.6%	-2.79 [-10.11 , 4.53]
Sudha 2019	75.25	12.96	59	81.6	15.43	60	4.6%	-6.35 [-11.47 , -1.23]
Szymanski 2006	83.6	55.6	46	96	71.5	41	3.6%	-12.40 [-39.55 , 14.75]
Szymanski 2019	58.7	43.8	44	66.9	57.4	47	3.9%	-8.20 [-29.10 , 12.70]
Villarruel 2007	112.8	46.56	35	147.8	76.8	37	3.4%	-35.00 [-64.16 , -5.84]
Subtotal (95% CI)			**2862**			**2768**	**100.0%**	**-21.43 [-31.85 , -11.02]**
Heterogeneity: Tau² = 602.22; Chi² = 647.51, df = 23 (P < 0.00001); I² = 96%								
Test for overall effect: Z = 4.03 (P < 0.0001)								
11.2.5 Adequate participant follow-up								
Aggarwal 2014	60	13.3	100	78	13.3	100	2.6%	-18.00 [-21.69 , -14.31]
Basu 2007	163.2	50.4	323	158.4	55.2	323	2.5%	4.80 [-3.35 , 12.95]
Basu 2009	122.9	27.8	186	173.5	30.5	185	2.6%	-50.60 [-56.54 , -44.66]
Bhat 2018	41.68	10.84	40	57.65	26.31	40	2.5%	-15.97 [-24.79 , -7.15]
Boudraa 2001	44.1	33.7	56	61.7	35.6	56	2.4%	-17.60 [-30.44 , -4.76]
Burande 2013	81.6	33.6	35	132	50.4	35	2.1%	-50.40 [-70.47 , -30.33]
Canani 2007	78.5	35.52	100	115.5	23.53	92	2.5%	-37.00 [-45.46 , -28.54]
Chen 2010	60.1	31.7	150	86.3	37.6	143	2.5%	-26.20 [-34.18 , -18.22]
Costa-Ribeiro 2003	38.3	3.78	61	39.1	4.6	63	2.6%	-0.80 [-2.28 , 0.68]
Dalgic 2011	74.64	43.44	60	81.84	33.12	60	2.3%	-7.20 [-21.02 , 6.62]
Das 2016	60	11.85	30	89	20	28	2.5%	-29.00 [-37.54 , -20.46]
Dinleyici 2014	70.7	26.1	64	103.8	28.4	63	2.5%	-33.10 [-42.59 , -23.61]
Dinleyici 2015a	60.4	24.5	29	74.3	15.3	31	2.4%	-13.90 [-24.32 , -3.48]
Dinleyici 2015b	75.4	33.1	220	99.8	32.5	143	2.5%	-24.40 [-31.29 , -17.51]
Dutta 2011	34	20.4	78	36.5	21.4	70	2.5%	-2.50 [-9.25 , 4.25]
El-Soud 2015	74.88	22.08	25	98.4	22.56	25	2.4%	-23.52 [-35.89 , -11.15]
Erdogan 2012	158.4	40.8	25	168	38.4	25	2.0%	-9.60 [-31.56 , 12.36]
Francavilla 2012	50.4	40.8	35	79.2	50.4	34	2.0%	-28.80 [-50.47 , -7.13]
Freedman 2015	71.1	78.3	61	63.5	64.3	62	1.8%	7.60 [-17.74 , 32.94]
Freedman 2018a	67.35	65.99	414	72.2	69.99	413	2.5%	-4.85 [-14.12 , 4.42]
Guarino 1997	76.8	34.61	52	141.6	33.26	48	2.3%	-64.80 [-78.10 , -51.50]

Analysis 11.2. (Continued)

Freedman 2018a	67.35	65.99	414	72.2	69.99	413	2.5%	-4.85 [-14.12 , 4.42]
Guarino 1997	76.8	34.61	52	141.6	33.26	48	2.3%	-64.80 [-78.10 , -51.50]
Hamid 2019	76.8	31.2	160	79.2	26.4	150	2.6%	-2.40 [-8.82 , 4.02]
Henker 2007a	70.3	23.52	55	104.9	9.12	58	2.5%	-34.60 [-41.24 , -27.96]
Henker 2008	57.6	19.47	75	136.8	18.8	76	2.6%	-79.20 [-85.31 , -73.09]
Huang 2014	43.2	38.4	82	69.6	33.6	77	2.4%	-26.40 [-37.60 , -15.20]
Isolauri 1994	36	16.8	21	55.2	19.2	21	2.4%	-19.20 [-30.11 , -8.29]
Jasinski 2002	74.6	47.76	45	133.4	53.76	52	2.1%	-58.80 [-79.00 , -38.60]
Javeed 2018	104.9	33.1	157	110.2	36.1	157	2.5%	-5.30 [-12.96 , 2.36]
Kianifar 2009	81.6	108.6	32	108	105.2	30	0.9%	-26.40 [-79.63 , 26.83]
Kowalska-Duplaga 2004	54.6	30	86	61.6	34	87	2.5%	-7.00 [-16.55 , 2.55]
Lee 2001	74.4	16.8	50	86.4	19.2	50	2.5%	-12.00 [-19.07 , -4.93]
Mao 2008	67.2	40.2	70	67.2	40.5	71	2.3%	0.00 [-13.32 , 13.32]
Narayanappa 2008	104.4	30.05	40	130.8	40.66	40	2.3%	-26.40 [-42.07 , -10.73]
Park 2017	105.12	30.96	28	134.64	29.52	29	2.3%	-29.52 [-45.23 , -13.81]
Riaz 2012	49.55	23.72	43	66.34	29.27	47	2.4%	-16.79 [-27.76 , -5.82]
Sarkar 2005	90.4	45	115	94.2	43.3	115	2.4%	-3.80 [-15.21 , 7.61]
Schnadower 2018	60.74	58.88	468	63.53	55.73	475	2.5%	-2.79 [-10.11 , 4.53]
Shornikova 1997a	64.8	52.8	59	91.2	67.2	64	2.0%	-26.40 [-47.67 , -5.13]
Shornikova 1997c	40.8	38.4	19	69.6	55.2	21	1.7%	-28.80 [-58.05 , 0.45]
Sudha 2019	75.25	12.96	59	81.6	15.43	60	2.6%	-6.35 [-11.47 , -1.23]
Szymanski 2006	83.6	55.6	46	96	71.5	41	1.8%	-12.40 [-39.55 , 14.75]
Vivatvakin 2006	38.4	16.8	36	69.6	40.8	35	2.3%	-31.20 [-45.79 , -16.61]
Xie 2013	132	38.4	50	139.2	40.8	50	2.3%	-7.20 [-22.73 , 8.33]
Subtotal (95% CI)			**3940**			**3845**	**100.0%**	**-20.93 [-27.24 , -14.62]**
Heterogeneity: Tau² = 395.15; Chi² = 1181.23, df = 42 (P < 0.00001); I² = 96%								
Test for overall effect: Z = 6.50 (P < 0.00001)								
11.2.6 Adequate outcome reporting								
Aggarwal 2014	60	13.3	100	78	13.3	100	2.1%	-18.00 [-21.69 , -14.31]
Basu 2007	163.2	50.4	323	158.4	55.2	323	2.1%	4.80 [-3.35 , 12.95]
Basu 2009	122.9	27.8	186	173.5	30.5	185	2.1%	-50.60 [-56.54 , -44.66]
Bhat 2018	41.68	10.84	40	57.65	26.31	40	2.1%	-15.97 [-24.79 , -7.15]
Boudraa 2001	44.1	33.7	56	61.7	35.6	56	2.0%	-17.60 [-30.44 , -4.76]
Burande 2013	81.6	33.6	35	132	50.4	35	1.7%	-50.40 [-70.47 , -30.33]
Burki 2017	77.52	31.42	100	140.16	43.54	100	2.0%	-62.64 [-73.16 , -52.12]
Canani 2007	78.5	35.52	100	115.5	23.53	92	2.1%	-37.00 [-45.46 , -28.54]
Chen 2010	60.1	31.7	150	86.3	37.6	143	2.1%	-26.20 [-34.18 , -18.22]
Costa-Ribeiro 2003	38.3	3.78	61	39.1	4.6	63	2.2%	-0.80 [-2.28 , 0.68]
Dalgic 2011	74.64	43.44	60	81.84	33.12	60	1.9%	-7.20 [-21.02 , 6.62]
Das 2016	60	11.85	30	89	20	28	2.1%	-29.00 [-37.54 , -20.46]
Dinleyici 2014	70.7	26.1	64	103.8	28.4	63	2.0%	-33.10 [-42.59 , -23.61]
Dinleyici 2015a	60.4	24.5	29	74.3	15.3	31	2.0%	-13.90 [-24.32 , -3.48]
Dinleyici 2015b	75.4	33.1	220	99.8	32.5	143	2.1%	-24.40 [-31.29 , -17.51]
Dutta 2011	34	20.4	78	36.5	21.4	70	2.1%	-2.50 [-9.25 , 4.25]
El-Soud 2015	74.88	22.08	25	98.4	22.56	25	2.0%	-23.52 [-35.89 , -11.15]
Erdogan 2012	158.4	40.8	25	168	38.4	25	1.7%	-9.60 [-31.56 , 12.36]
Francavilla 2012	50.4	40.8	35	79.2	50.4	34	1.7%	-28.80 [-50.47 , -7.13]
Freedman 2015	71.1	78.3	61	63.5	64.3	62	1.5%	7.60 [-17.74 , 32.94]
Freedman 2018a	67.35	65.99	414	72.2	69.99	413	2.1%	-4.85 [-14.12 , 4.42]
Guandalini 2000	58.3	27.6	147	71.9	35.8	140	2.1%	-13.60 [-21.02 , -6.18]
Guarino 1997	76.8	34.61	52	141.6	33.26	48	1.9%	-64.80 [-78.10 , -51.50]
Hamid 2019	76.8	31.2	160	79.2	26.4	150	2.1%	-2.40 [-8.82 , 4.02]
Henker 2007a	70.3	23.52	55	104.9	9.12	58	2.1%	-34.60 [-41.24 , -27.96]
Henker 2008	57.6	19.47	75	136.8	18.8	76	2.1%	-79.20 [-85.31 , -73.09]
Huang 2014	43.2	38.4	82	69.6	33.6	77	2.0%	-26.40 [-37.60 , -15.20]
Jasinski 2002	74.6	47.76	45	133.4	53.76	52	1.7%	-58.80 [-79.00 , -38.60]
Javeed 2018	104.9	33.1	157	110.2	36.1	157	2.1%	-5.30 [-12.96 , 2.36]
Kurugol 2005	112.8	60	100	132	76.8	100	1.8%	-19.20 [-38.30 , -0.10]
Lee 2001	74.4	16.8	50	86.4	19.2	50	2.1%	-12.00 [-19.07 , -4.93]
Mao 2008	67.2	40.2	70	67.2	40.5	71	1.9%	0.00 [-13.32 , 13.32]
Narayanappa 2008	104.4	30.05	40	130.8	40.66	40	1.9%	-26.40 [-42.07 , -10.73]
Nixon 2012	67.7	36	63	74	39.5	66	2.0%	-6.30 [-19.33 , 6.73]
Pant 1996	45.6	14.4	14	79.2	55.2	12	1.3%	-33.60 [-65.73 , -1.47]
Park 2017	105.12	30.96	28	134.64	29.52	29	1.9%	-29.52 [-45.23 , -13.81]
Riaz 2012	49.55	23.72	43	66.34	29.27	47	2.0%	-16.79 [-27.76 , -5.82]

Analysis 11.2. (Continued)

Pant 1996	45.6	14.4	14	79.2	55.2	12	1.3%	-33.60 [-65.73 , -1.47]
Park 2017	105.12	30.96	28	134.64	29.52	29	1.9%	-29.52 [-45.23 , -13.81]
Riaz 2012	49.55	23.72	43	66.34	29.27	47	2.0%	-16.79 [-27.76 , -5.82]
Ritchie 2010	52.4	49.8	33	51.2	42.4	31	1.6%	1.20 [-21.42 , 23.82]
Rosenfeldt 2002a	81.5	37.3	30	101.1	47.6	39	1.7%	-19.60 [-39.63 , 0.43]
Rosenfeldt 2002b	75.9	39.7	24	115.7	85	19	1.0%	-39.80 [-81.19 , 1.59]
Sarkar 2005	90.4	45	115	94.2	43.3	115	2.0%	-3.80 [-15.21 , 7.61]
Schnadower 2018	60.74	58.88	468	63.53	55.73	475	2.1%	-2.79 [-10.11 , 4.53]
Shornikova 1997a	64.8	52.8	59	91.2	67.2	64	1.7%	-26.40 [-47.67 , -5.13]
Shornikova 1997b	36	26.4	21	60	36	25	1.8%	-24.00 [-42.07 , -5.93]
Shornikova 1997c	40.8	38.4	19	69.6	55.2	21	1.4%	-28.80 [-58.05 , 0.45]
Simadibrata 2013	58.74	38.54	38	83.37	49.83	38	1.7%	-24.63 [-44.66 , -4.60]
Sudha 2019	75.25	12.96	59	81.6	15.43	60	2.1%	-6.35 [-11.47 , -1.23]
Szymanski 2006	83.6	55.6	46	96	71.5	41	1.5%	-12.40 [-39.55 , 14.75]
Szymanski 2019	58.7	43.8	44	66.9	57.4	47	1.7%	-8.20 [-29.10 , 12.70]
Teran 2009	57.1	25.4	25	74.6	26.6	25	1.9%	-17.50 [-31.92 , -3.08]
Villarruel 2007	112.8	46.56	35	147.8	76.8	37	1.4%	-35.00 [-64.16 , -5.84]
Vivatvakin 2006	38.4	16.8	36	69.6	40.8	35	1.9%	-31.20 [-45.79 , -16.61]
Xie 2013	132	38.4	50	139.2	40.8	50	1.9%	-7.20 [-22.73 , 8.33]
Subtotal (95% CI)			**4475**			**4386**	**100.0%**	**-21.60 [-27.39 , -15.81]**
Heterogeneity: Tau² = 402.59; Chi² = 1280.24, df = 52 (P < 0.00001); I² = 96%								
Test for overall effect: Z = 7.31 (P < 0.00001)								
11.2.7 Low risk of bias for all parameters								
Basu 2007	163.2	50.4	323	158.4	55.2	323	17.1%	4.80 [-3.35 , 12.95]
Basu 2009	122.9	27.8	186	173.5	30.5	185	17.4%	-50.60 [-56.54 , -44.66]
Dutta 2011	34	20.4	78	36.5	21.4	70	17.3%	-2.50 [-9.25 , 4.25]
Freedman 2015	71.1	78.3	61	63.5	64.3	62	13.9%	7.60 [-17.74 , 32.94]
Freedman 2018a	67.35	65.99	414	72.2	69.99	413	17.0%	-4.85 [-14.12 , 4.42]
Schnadower 2018	60.74	58.88	468	63.53	55.73	475	17.2%	-2.79 [-10.11 , 4.53]
Subtotal (95% CI)			**1530**			**1528**	**100.0%**	**-8.64 [-29.38 , 12.10]**
Heterogeneity: Tau² = 635.50; Chi² = 192.05, df = 5 (P < 0.00001); I² = 97%								
Test for overall effect: Z = 0.82 (P = 0.41)								



Comparison 12. Publication decade

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
12.1 Diarrhoea lasting ≥ 48 hours	36		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
12.1.1 1980s	4	187	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.34, 0.74]
12.1.2 1990s	7	589	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.54, 0.86]
12.1.3 2000s	10	1305	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.52, 0.74]
12.1.4 2010s	15	3972	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.63, 0.98]
12.2 Mean duration of diarrhoea	56		Mean Difference (IV, Random, 95% CI)	Subtotals only
12.2.1 1990s	6	377	Mean Difference (IV, Random, 95% CI)	-33.18 [-51.33, -15.03]
12.2.2 2000s	22	3471	Mean Difference (IV, Random, 95% CI)	-24.08 [-36.09, -12.07]
12.2.3 2010s	28	5290	Mean Difference (IV, Random, 95% CI)	-17.15 [-22.27, -12.03]

Analysis 12.1. Comparison 12: Publication decade, Outcome 1: Diarrhoea lasting ≥ 48 hours

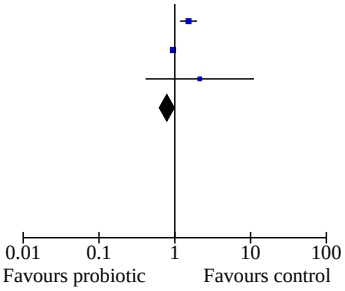
Study or Subgroup	Favours probiotic Events	Total	Favours control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
12.1.1 1980s						
Bruno 1981	6	25	17	24	21.9%	0.34 [0.16 , 0.71]
Bruno 1983	3	10	7	11	12.3%	0.47 [0.17 , 1.34]
D'Apuzzo 1982	4	21	10	18	14.0%	0.34 [0.13 , 0.91]
Wunderlich 1989	19	40	27	38	51.9%	0.67 [0.46 , 0.98]
Subtotal (95% CI)		**96**		**91**	**100.0%**	**0.50 [0.34 , 0.74]**
Total events:	32		61			
Heterogeneity: Tau² = 0.04; Chi² = 3.84, df = 3 (P = 0.28); I² = 22%						
Test for overall effect: Z = 3.44 (P = 0.0006)						
12.1.2 1990s						
Bhatnagar 1998	27	47	26	49	19.9%	1.08 [0.76 , 1.55]
Buydens 1996	57	93	88	92	31.7%	0.64 [0.54 , 0.76]
Cetina-Sauri 1994	41	65	58	65	29.4%	0.71 [0.58 , 0.87]
Hernandez 1998	5	25	11	25	5.7%	0.45 [0.18 , 1.12]
Isolauri 1994	2	21	9	21	2.6%	0.22 [0.05 , 0.91]
Shornikova 1997b	6	21	11	25	6.8%	0.65 [0.29 , 1.46]
Shornikova 1997c	3	19	11	21	3.9%	0.30 [0.10 , 0.92]
Subtotal (95% CI)		**291**		**298**	**100.0%**	**0.68 [0.54 , 0.86]**
Total events:	141		214			
Heterogeneity: Tau² = 0.04; Chi² = 12.44, df = 6 (P = 0.05); I² = 52%						
Test for overall effect: Z = 3.25 (P = 0.001)						
12.1.3 2000s						
Boudraa 2001	9	56	23	56	5.2%	0.39 [0.20 , 0.77]
Costa-Ribeiro 2003	31	61	45	63	13.1%	0.71 [0.53 , 0.95]
Guandalini 2000	78	147	90	140	16.2%	0.83 [0.68 , 1.00]
Henker 2007a	21	55	32	58	9.8%	0.69 [0.46 , 1.04]
Henker 2008	34	75	49	76	12.9%	0.70 [0.52 , 0.95]
Jasinski 2002	25	45	46	52	13.5%	0.63 [0.48 , 0.83]
Kurugol 2005	20	100	55	100	9.3%	0.36 [0.24 , 0.56]
Teran 2009	7	25	16	25	5.0%	0.44 [0.22 , 0.88]
Urganci 2001	28	50	42	50	13.7%	0.67 [0.51 , 0.88]
Vivatvakin 2006	2	36	11	35	1.4%	0.18 [0.04 , 0.74]
Subtotal (95% CI)		**650**		**655**	**100.0%**	**0.62 [0.52 , 0.74]**
Total events:	255		409			
Heterogeneity: Tau² = 0.04; Chi² = 21.07, df = 9 (P = 0.01); I² = 57%						
Test for overall effect: Z = 5.31 (P < 0.00001)						
12.1.4 2010s						
Burki 2017	60	100	80	100	7.7%	0.75 [0.62 , 0.90]
Chen 2010	64	150	97	143	7.5%	0.63 [0.51 , 0.78]
Correa 2011	39	90	69	86	7.3%	0.54 [0.42 , 0.70]
Dinleyici 2014	32	64	60	63	7.3%	0.53 [0.41 , 0.67]
Dinleyici 2015a	13	29	27	31	6.2%	0.51 [0.34 , 0.79]
Dinleyici 2015b	141	220	120	143	7.9%	0.76 [0.68 , 0.86]
Freedman 2018a	228	414	225	413	7.9%	1.01 [0.89 , 1.14]
Javeed 2018	157	157	157	157	8.1%	1.00 [0.99 , 1.01]
Maity 2019	18	30	30	30	7.1%	0.61 [0.45 , 0.81]
Rerksuppaphol 2010	4	23	11	22	3.1%	0.35 [0.13 , 0.93]
Ritchie 2010	13	33	12	31	5.0%	1.02 [0.55 , 1.88]
Schnadower 2018	243	468	251	475	7.9%	0.98 [0.87 , 1.11]
Sirsat 2017	82	145	54	145	7.3%	1.52 [1.18 , 1.96]
Sudha 2019	54	59	58	60	8.0%	0.95 [0.86 , 1.04]

Analysis 12.1. (Continued)

Sirsat 2017	82	145	54	145	7.3%	1.52 [1.18 , 1.96]
Sudha 2019	54	59	58	60	8.0%	0.95 [0.86 , 1.04]
Szymanski 2019	4	44	2	47	1.5%	2.14 [0.41 , 11.09]
Subtotal (95% CI)		**2026**		**1946**	**100.0%**	**0.78 [0.63 , 0.98]**
Total events:	1152		1253			

Heterogeneity: Tau² = 0.16; Chi² = 528.13, df = 14 (P < 0.00001); I² = 97%

Test for overall effect: Z = 2.14 (P = 0.03)



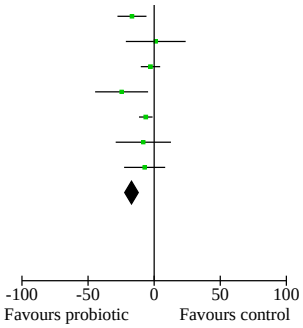
Analysis 12.2. Comparison 12: Publication decade, Outcome 2: Mean duration of diarrhoea

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
12.2.1 1990s								
Guarino 1997	76.8	34.61	52	141.6	33.26	48	19.2%	-64.80 [-78.10 , -51.50]
Isolauri 1994	36	16.8	21	55.2	19.2	21	19.9%	-19.20 [-30.11 , -8.29]
Pant 1996	45.6	14.4	14	79.2	55.2	12	12.8%	-33.60 [-65.73 , -1.47]
Shornikova 1997a	64.8	52.8	59	91.2	67.2	64	16.6%	-26.40 [-47.67 , -5.13]
Shornikova 1997b	36	26.4	21	60	36	25	17.7%	-24.00 [-42.07 , -5.93]
Shornikova 1997c	40.8	38.4	19	69.6	55.2	21	13.8%	-28.80 [-58.05 , 0.45]
Subtotal (95% CI)			**186**			**191**	**100.0%**	**-33.18 [-51.33 , -15.03]**
Heterogeneity: Tau² = 399.86; Chi² = 29.44, df = 5 (P < 0.0001); I² = 83%								
Test for overall effect: Z = 3.58 (P = 0.0003)								
12.2.2 2000s								
Basu 2007	163.2	50.4	323	158.4	55.2	323	4.9%	4.80 [-3.35 , 12.95]
Basu 2009	122.9	27.8	186	173.5	30.5	185	5.0%	-50.60 [-56.54 , -44.66]
Boudraa 2001	44.1	33.7	56	61.7	35.6	56	4.8%	-17.60 [-30.44 , -4.76]
Canani 2007	78.5	35.52	100	115.5	23.53	92	4.9%	-37.00 [-45.46 , -28.54]
Costa-Ribeiro 2003	38.3	3.78	61	39.1	4.6	63	5.0%	-0.80 [-2.28 , 0.68]
Guandalini 2000	58.3	27.6	147	71.9	35.8	140	5.0%	-13.60 [-21.02 , -6.18]
Henker 2007a	70.3	23.52	55	104.9	9.12	58	5.0%	-34.60 [-41.24 , -27.96]
Henker 2008	57.6	19.47	75	136.8	18.8	76	5.0%	-79.20 [-85.31 , -73.09]
Jasinski 2002	74.6	47.76	45	133.4	53.76	52	4.4%	-58.80 [-79.00 , -38.60]
Kianifar 2009	81.6	108.6	32	108	105.2	30	2.5%	-26.40 [-79.63 , 26.83]
Kowalska-Duplaga 2004	54.6	30	86	61.6	34	87	4.9%	-7.00 [-16.55 , 2.55]
Kurugol 2005	112.8	60	100	132	76.8	100	4.5%	-19.20 [-38.30 , -0.10]
Lee 2001	74.4	16.8	50	86.4	19.2	50	5.0%	-12.00 [-19.07 , -4.93]
Mao 2008	67.2	40.2	70	67.2	40.5	71	4.8%	0.00 [-13.32 , 13.32]
Narayanappa 2008	104.4	30.05	40	130.8	40.66	40	4.7%	-26.40 [-42.07 , -10.73]
Rosenfeldt 2002a	81.5	37.3	30	101.1	47.6	39	4.4%	-19.60 [-39.63 , 0.43]
Rosenfeldt 2002b	75.9	39.7	24	115.7	85	19	3.2%	-39.80 [-81.19 , 1.59]
Sarkar 2005	90.4	45	115	94.2	43.3	115	4.8%	-3.80 [-15.21 , 7.61]
Szymanski 2006	83.6	55.6	46	96	71.5	41	4.0%	-12.40 [-39.55 , 14.75]
Teran 2009	57.1	25.4	25	74.6	26.6	25	4.7%	-17.50 [-31.92 , -3.08]
Villarruel 2007	112.8	46.56	35	147.8	76.8	37	3.9%	-35.00 [-64.16 , -5.84]
Vivatvakin 2006	38.4	16.8	36	69.6	40.8	35	4.7%	-31.20 [-45.79 , -16.61]
Subtotal (95% CI)			**1737**			**1734**	**100.0%**	**-24.08 [-36.09 , -12.07]**
Heterogeneity: Tau² = 743.78; Chi² = 974.80, df = 21 (P < 0.00001); I² = 98%								
Test for overall effect: Z = 3.93 (P < 0.0001)								
12.2.3 2010s								
Aggarwal 2014	60	13.3	100	78	13.3	100	4.5%	-18.00 [-21.69 , -14.31]
Bhat 2018	41.68	10.84	40	57.65	26.31	40	4.0%	-15.97 [-24.79 , -7.15]
Burande 2013	81.6	33.6	35	132	50.4	35	2.7%	-50.40 [-70.47 , -30.33]
Burki 2017	77.52	31.42	100	140.16	43.54	100	3.8%	-62.64 [-73.16 , -52.12]
Chen 2010	60.1	31.7	150	86.3	37.6	143	4.1%	-26.20 [-34.18 , -18.22]
Dalgic 2011	74.64	43.44	60	81.84	33.12	60	3.4%	-7.20 [-21.02 , 6.62]
Das 2016	60	11.85	30	89	20	28	4.1%	-29.00 [-37.54 , -20.46]
Dinleyici 2014	70.7	26.1	64	103.8	28.4	63	4.0%	-33.10 [-42.59 , -23.61]
Dinleyici 2015a	60.4	24.5	29	74.3	15.3	31	3.9%	-13.90 [-24.32 , -3.48]
Dinleyici 2015b	75.4	33.1	220	99.8	32.5	143	4.2%	-24.40 [-31.29 , -17.51]
Dutta 2011	34	20.4	78	36.5	21.4	70	4.2%	-2.50 [-9.25 , 4.25]
El-Soud 2015	74.88	22.08	25	98.4	22.56	25	3.6%	-23.52 [-35.89 , -11.15]
Erdogan 2012	158.4	40.8	25	168	38.4	25	2.5%	-9.60 [-31.56 , 12.36]
Francavilla 2012	50.4	40.8	35	79.2	50.4	34	2.5%	-28.80 [-50.47 , -7.13]
Freedman 2015	71.1	78.3	61	63.5	64.3	62	2.2%	7.60 [-17.74 , 32.94]
Freedman 2018a	67.35	65.99	414	72.2	69.99	413	4.0%	-4.85 [-14.12 , 4.42]
Hamid 2019	76.8	31.2	160	79.2	26.4	150	4.3%	-2.40 [-8.82 , 4.02]
Huang 2014	43.2	38.4	82	69.6	33.6	77	3.8%	-26.40 [-37.60 , -15.20]
Javeed 2018	104.9	33.1	157	110.2	36.1	157	4.2%	-5.30 [-12.96 , 2.36]
Nixon 2012	67.7	36	63	74	39.5	66	3.5%	-6.30 [-19.33 , 6.73]
Park 2017	105.12	30.96	28	134.64	29.52	29	3.2%	-29.52 [-45.23 , -13.81]
Riaz 2012	49.55	23.72	43	66.34	29.27	47	3.8%	-16.79 [-27.76 , -5.82]
Ritchie 2010	52.4	49.8	33	51.2	42.4	31	2.4%	1.20 [-21.42 , 23.82]

Analysis 12.2. (Continued)

Riaz 2012	49.55	23.72	43	66.34	29.27	47	3.8%	-16.79 [-27.76 , -5.82]
Ritchie 2010	52.4	49.8	33	51.2	42.4	31	2.4%	1.20 [-21.42 , 23.82]
Schnadower 2018	60.74	58.88	468	63.53	55.73	475	4.2%	-2.79 [-10.11 , 4.53]
Simadibrata 2013	58.74	38.54	38	83.37	49.83	38	2.7%	-24.63 [-44.66 , -4.60]
Sudha 2019	75.25	12.96	59	81.6	15.43	60	4.4%	-6.35 [-11.47 , -1.23]
Szymanski 2019	58.7	43.8	44	66.9	57.4	47	2.6%	-8.20 [-29.10 , 12.70]
Xie 2013	132	38.4	50	139.2	40.8	50	3.2%	-7.20 [-22.73 , 8.33]
Subtotal (95% CI)			**2691**			**2599**	**100.0%**	**-17.15 [-22.27 , -12.03]**

Heterogeneity: Tau² = 149.11; Chi² = 213.69, df = 27 (P < 0.00001); I² = 87%
Test for overall effect: Z = 6.56 (P < 0.00001)



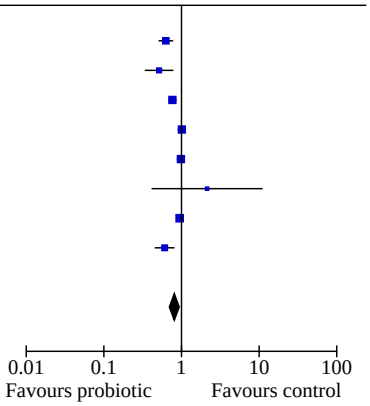
Comparison 13. Prospective trial registration

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13.1 Diarrhoea lasting ≥ 48 hours	8	2756	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.70, 0.93]
13.2 Mean duration of diarrhoea	12	3437	Mean Difference (IV, Random, 95% CI)	-16.43 [-22.43, -10.43]

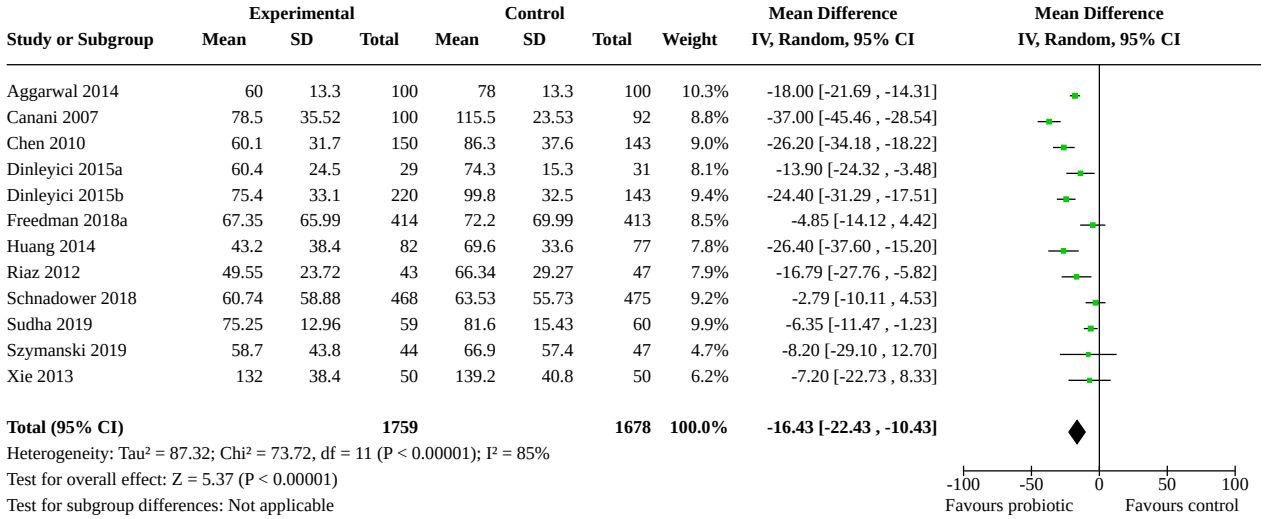
Analysis 13.1. Comparison 13: Prospective trial registration, Outcome 1: Diarrhoea lasting ≥ 48 hours

	Experimental		Control			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Chen 2010	64	150	97	143	13.4%	0.63 [0.51 , 0.78]	
Dinleyici 2015a	13	29	27	31	7.2%	0.51 [0.34 , 0.79]	
Dinleyici 2015b	141	220	120	143	16.8%	0.76 [0.68 , 0.86]	
Freedman 2018a	228	414	225	413	16.7%	1.01 [0.89 , 1.14]	
Schnadower 2018	243	468	251	475	16.8%	0.98 [0.87 , 1.11]	
Szymanski 2019	4	44	2	47	0.7%	2.14 [0.41 , 11.09]	
Sudha 2019	54	59	58	60	17.7%	0.95 [0.86 , 1.04]	
Maity 2019	18	30	30	30	10.7%	0.61 [0.45 , 0.81]	
Total (95% CI)		**1414**		**1342**	**100.0%**	**0.81 [0.70 , 0.93]**	
Total events:	765		810				

Heterogeneity: Tau² = 0.03; Chi² = 38.20, df = 7 (P < 0.00001); I² = 82%
Test for overall effect: Z = 2.88 (P = 0.004)
Test for subgroup differences: Not applicable



Analysis 13.2. Comparison 13: Prospective trial registration, Outcome 2: Mean duration of diarrhoea



APPENDICES

Appendix 1. Detailed search strategy

Search set	CIDG SR[a]	CENTRAL	MEDLINE[b]	Embase[b]	LILACS[b]
1	Diarrhea*	DIARRHEA	DIARRHEA	INFECTIOUS DIARRHEA	Diarrhea$
2	Diarrhoea*	Diarrhoea*	Diarrhoea*	Diarrhoea*	Diarrhoea$
3	1 or 2	1 or 2	1 or 2	1 or 2	1 or 2
4	Probiotic*	Probiotic*	PROBIOTICS	PROBIOTIC AGENT	Probiotic$
5	Lactobacill*	Lactobacill*	Lactobacill*	Lactobacill$	Lactobacill$
6	Lactococc*	Lactococc*	Lactococc*	Lactococc$	Lactococc$
7	Bifidobacter*	Bifidobacter*	Bifidobacter*	Bifidobacter$	Bifidobacter$
8	Enterococc*	Enterococc*	Enterococc*	Enterococc$	Enterococc$
9	Streptococc*	Streptococc*	Streptococc*	Streptococc$	Streptococc$
10	saccharomyces	saccharomyces	saccharomyces	saccharomyces	saccharomyces
11	4 or 5 or 6 or 7 or 8 or 9 or 10	4 or 5 or 6 or 7 or 8 or 9 or 10	4 or 5 or 6 or 7 or 8 or 9 or 10	4 or 5 or 6 or 7 or 8 or 9 or 10	4 or 5 or 6 or 7 or 8 or 9 or 10
12	3 and 11	3 and 11	3 and 11	3 and 11	3 and 11
13			Limit 12 to Humans	Limit 12 to Human	

Footnotes

[a]Cochrane Infectious Diseases Group Specialized Register.
[b]Search terms used in combination with the search strategy for retrieving trials developed by Cochrane (Higgins 2008); upper case: MeSH or EMTREE heading; lower case: free text term.

WHAT'S NEW

Date	Event	Description
1 December 2020	New search has been performed	We updated the search to 17 December 2019, and have included 36 new studies in this review update. In this review, only published, randomized controlled trials of live probiotics were included. Seventeen trials that were unpublished, were quasi-randomized, assessed killed probiotics, or had no usable outcome data that were included in Allen 2010 were excluded. We revised the outcomes according to a consensus statement regarding a core outcome measurement set for clinical trials in acute diarrhoea (Karas 2016). To better assess the quality of research methods and publication bias, we have included analyses according to the decade of trial publication and trial registration.
1 December 2020	New citation required and conclusions have changed	In our conclusions, under Implications for practice, we now consider that our findings do not support the use of probiotics for treatment of acute diarrhoea. Under Implications for research, we have highlighted that limiting inclusion of trials to those registered in a clinical trials database may improve the reliability of study findings.

HISTORY

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

Date	Event	Description
9 November 2010	Amended	Detailed search strategy added to appendices
11 August 2010	New citation required but conclusions have not changed	Title changed ("acute" added) to emphasize that persistent diarrhoea is not considered. The authorship of the update has changed due to the untimely death of Dr Okoko
11 August 2010	New search has been performed	The table showing clinical variability among studies has been removed and this information added to the Characteristics of included studies table. A table has been added to show the marked statistical heterogeneity in primary outcomes and subgroup analyses (Table 1) The following secondary outcomes have been removed as they were uncommon or were not reported: need for unscheduled intravenous (IV) rehydration after randomization; death; adverse events, such as vomiting; withdrawal from the study. Details re-

Date	Event	Description
		garding adverse events and reasons for withdrawal are included in the "Details of included studies" table
22 July 2008	Amended	Converted to new review format
8 December 2007	New citation required and conclusions have changed	Substantive amendments made

CONTRIBUTIONS OF AUTHORS

Shelui Collinson and Stephen Allen identified articles for inclusion in the review. Leonila Dans, Germana Gregorio, April Padua, and Shelui Collinson assessed study quality, and Stephen Allen settled any disagreements. Shelui Collinson, Andrew Deans, and Stephen Allen extracted data. Chao Li advised on statistical analysis, assessment of publication bias, and NMA. Shelui Collinson wrote the first draft of the review. Stephen Allen took the main responsibility for analysis and for writing the final version of the review. All reviewers contributed to the final version.

DECLARATIONS OF INTEREST

Shelui Collinson has no known conflicts of interest.

Andrew Deans has no known conflicts of interest.

April Padua has no known conflicts of interest.

Germana V Gregorio has no known conflicts of interest.

Chao Li has no known conflicts of interest.

Leonila F Dans has no known conflicts of interest.

Stephen J Allen: travel and accommodation expenses to attend the Nutricia Neocate Syneo Meeting (November 2016) at the Nutricia Utrecht Research Centre were paid.

SOURCES OF SUPPORT

Internal sources

- Liverpool School of Tropical Medicine, UK

External sources

- Foreign, Commonwealth and Development Office (FCDO), UK

  Project number 300342-104

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Differences between review update (2010) and review update (2020)

This review is a substantial update of the original version, Allen 2003, and its update (Allen 2010).

In this review, only published, randomized controlled trials of live probiotics were included. Seventeen trials that were unpublished, were quasi-randomized, assessed killed probiotics, or had no usable outcome data that were included in Allen 2010 were excluded.

We revised the outcomes according to a consensus statement regarding a core outcome measurement set for clinical trials in acute diarrhoea (Karas 2016).

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Bias; Diarrhea [*therapy]; Probiotics [*therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Adolescent; Adult; Child; Child, Preschool; Humans; Infant