




PROBIOTICS FOR THE PREVENTION OF PEDIATRIC ANTIBIOTIC-ASSOCIATED DIARRHEA**Johnston Bradley C, Goldenberg Joshua Z, Vandvik Per O, Sun Xin, Guyatt Gordon H**

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ABSTRACT**Background**

Antibiotics alter the microbial balance within the gastrointestinal tract. Probiotics may prevent antibiotic-associated diarrhea (AAD) via restoration of the gut microflora. Antibiotics are prescribed frequently in children and AAD is common in this population.

Objective

The primary objectives were to assess the efficacy and safety of probiotics (any specified strain or dose) used for the prevention of AAD in children.

Criteria for considering studies for this review

MEDLINE, EMBASE, CENTRAL, CINAHL, AMED, and the Web of Science (inception to May 2010) were searched along with specialized registers including the Cochrane IBD/FBD review group, CISCOM (Centralized Information Service for Complementary Medicine), NHS Evidence, the International Bibliographic Information on Dietary Supplements as well as trial registries. Letters were sent to authors of included trials, nutra/pharmaceutical companies, and experts in the field requesting additional information on ongoing or unpublished trials. Conference proceedings, dissertation abstracts, and reference lists from included and relevant articles were also searched.

Selection criteria

Randomized, parallel, controlled trials in children (0 to 18 years) receiving antibiotics, that compare probiotics to placebo, active alternative prophylaxis, or no treatment and measure the incidence of diarrhea secondary to antibiotic use were considered for inclusion.

Data collection and analysis

Study selection, data extraction as well as methodological quality assessment using the risk of bias instrument was conducted independently and in duplicate by two authors. Dichotomous data (incidence of diarrhea, adverse events) were combined using a pooled relative risk and risk difference (adverse events), and continuous data (mean duration of diarrhea, mean daily stool frequency) as weighted mean differences, along with their corresponding 95% confidence intervals. For overall pooled results on the incidence of diarrhea, sensitivity analyses included available case versus extreme-plausible analyses and random- versus fixed-effect models. To explore possible explanations for heterogeneity, a priori subgroup analysis were conducted on probiotic strain, dose, definition of antibiotic-associated diarrhea, antibiotic agent as well as risk of bias.

Main results

Sixteen studies (3432 participants) met the inclusion criteria. Trials included treatment with either *Bacillus* spp., *Bifidobacterium* spp., *Lactobacilli* spp., *Lactococcus* spp., *Leuconostoc cremoris*, *Saccharomyces* spp., or *Streptococcus* spp., alone or in combination. Nine studies used a single strain probiotic agent, four combined two probiotic strains, one combined three probiotic strains, one product included ten probiotic agents, and one study included two probiotic arms that used three and two strains respectively. The risk of bias was determined to be high in 8 studies and low in 8 studies. Available case (patients who did not complete the studies were not included in the analysis) results from 15/16 trials reporting on the incidence of diarrhea show a large, precise benefit from probiotics compared to active, placebo or no treatment control. The incidence of AAD in the probiotic group was 9% compared to 18% in the control group (2874 participants; RR 0.52; 95% CI 0.38 to 0.72; I² = 56%). This benefit was not statistically significant in an extreme plausible (60% of children loss to follow-up in probiotic group and 20% loss to follow-up in the control group had diarrhea) intention to treat (ITT) sensitivity analysis. The incidence of AAD in the probiotic group was 16% compared to 18% in the control group (3392 participants; RR 0.81; 95% CI 0.63 to 1.04; I² = 59%). An a priori available case subgroup analysis exploring heterogeneity indicated that high dose (≥5 billion CFUs/day) is more effective than low probiotic dose (< 5 billion CFUs/day), interaction P value = 0.010. For the high dose studies the incidence of AAD in the probiotic group was 8% compared to 22% in the control group (1474 participants; RR 0.40; 95% CI 0.29 to 0.55). For the low dose studies the

incidence of AAD in the probiotic group was 8% compared to 11% in the control group (1382 participants; RR 0.80; 95% CI 0.53 to 1.21). An extreme plausible ITT subgroup analysis was marginally significant for high dose probiotics. For the high dose studies the incidence of AAD in the probiotic group was 17% compared to 22% in the control group (1776 participants; RR 0.72; 95% CI 0.53 to 0.99; I² = 58%). None of the 11 trials (n = 1583) that reported on adverse events documented any serious adverse events. Meta-analysis excluded all but an extremely small non-significant difference in adverse events between treatment and control (RD 0.00; 95% CI -0.01 to 0.02).

Authors' conclusions

Despite heterogeneity in probiotic strain, dose, and duration, as well as in study quality, the overall evidence suggests a protective effect of probiotics in preventing AAD. Using 11 criteria to evaluate the credibility of the subgroup analysis on probiotic dose, the results indicate that the subgroup effect based on dose (≥ 5 billion CFU/day) was credible. Based on high-dose probiotics, the number needed to treat (NNT) to prevent one case of diarrhea is seven (NNT 7; 95% CI 6 to 10). However, a GRADE analysis indicated that the overall quality of the evidence for the primary endpoint (incidence of diarrhea) was low due to issues with risk of bias (due to high loss to follow-up) and imprecision (sparse data, 225 events). The benefit for high dose probiotics (*Lactobacillus rhamnosus* or *Saccharomyces boulardii*) needs to be confirmed by a large well-designed randomized trial. More refined trials are also needed that test strain specific probiotics and evaluate the efficacy (e.g. incidence and duration of diarrhea) and safety of probiotics with limited losses to follow-up. It is premature to draw conclusions about the efficacy and safety of other probiotic agents for pediatric AAD. Future trials would benefit from a standard and valid outcomes to measure AAD.

PLAIN LANGUAGE SUMMARY

Antibiotic-associated diarrhea (AAD) occurs when antibiotics disturb the natural balance of "good" and "bad" bacteria in the intestinal tract causing harmful bacteria to multiply beyond their normal numbers. The symptoms of AAD include frequent watery bowel movements and crampy abdominal pain. Probiotics are found in dietary supplements or yogurts and contain potentially beneficial bacteria or yeast. Probiotics may restore the natural balance of bacteria in the intestinal tract. Sixteen studies were reviewed and provide the best available evidence. The studies tested 3432 children (2 weeks to 17 years of age) who were receiving probiotics co-administered with antibiotics to prevent AAD. The participants received probiotics (*Lactobacilli* spp., *Bifidobacterium* spp., *Streptococcus* spp., or *Saccharomyces boulardii* alone or in combination), placebo (pills not including probiotics), other treatments thought to prevent AAD (i.e. diosmectite or infant formula) or no treatment. The studies were short-term, ranging in length from 10 days to 3 months. Analyses showed that probiotics may be effective for preventing AAD. Probiotics were generally well tolerated, and minor side effects occurred infrequently, with no significant difference between probiotic and control groups. Side effects reported in the studies include rash, nausea, gas, flatulence, vomiting, increased phlegm, chest pain, constipation, taste disturbance, and low appetite. The current data suggest that *Lactobacillus rhamnosus* and *Saccharomyces boulardii* at a high dosage of 5 to 40 billion CFU/day may prevent the onset of AAD, with no serious side effects documented in otherwise healthy children. This benefit for high dose probiotics needs to be confirmed by a large well designed randomized study. No conclusions about the effectiveness and safety of other probiotic agents for pediatric AAD can be drawn. More refined studies are also needed that evaluate strain specific probiotics and report both the effectiveness (e.g. incidence and duration of diarrhea) and safety of probiotics.

WHAT'S NEW

What's new

Last assessed as up-to-date: 24 May 2010.

Date	Event	Description
3 January 2011	New citation required and conclusions have changed	Substantively updated review with new conclusions and new authors
3 January 2011	New search has been performed	New search, new studies added

BACKGROUND

ANTIBIOTIC-ASSOCIATED DIARRHEA

More than 400 species of bacteria inhabit the human gut, and a balance of these micro-organisms is important for normal gastrointestinal function ([Madsen 2001](#)). Antibiotic treatment may disturb the colonization resistance of gastrointestinal flora, resulting in a range of symptoms, most notably, diarrhea. In particular, antibiotics such as aminopenicillins, cephalosporins and clindamycin that act on anaerobes are most commonly associated with diarrhea ([Wistrom 2001](#); [Owens 2008](#); [McFarland 2008](#)). In addition to frequent watery bowel movements, urgency and crampy abdominal pain, antibiotic-associated diarrhea (AAD) is associated with altered intestinal microflora, mucosal integrity and vitamin/mineral metabolism ([Saavedra 1999](#)). If severe, AAD may lead to electrolyte disturbances, volume depletion, pseudomembranous colitis, toxic megacolon and possibly death ([Berrington 2004](#); [Arvola 1999](#)). Reports in the general population indicate that the incidence of AAD ranges from 5 to 62%, occurring at any point from the initiation of therapy to two months after the end of treatment ([LaRosa 2003](#); [Wistrom 2001](#); [McFarland 1998](#); [McFarland 2008](#)). The incidence of diarrhea in children receiving broad spectrum antibiotics has been reported in the range of 11 to 40% ([Turck 2003](#); [Eltner 1983](#)).

The overgrowth of many enteropathogens has been associated with antibiotic-induced diarrhea. *Clostridium difficile* (*C. difficile*) overgrowth is the bacterial agent most associated with AAD ([McFarland 2008](#); [McFarland 1998](#); [Bartlett 1978](#)). *C. difficile* diarrhea is associated with the most serious adverse events, and occurs most often in older, immunocompromised, hospitalized adults, but also occurs in children ([Gogate 2005](#)).

The definition of AAD varies across trials. Although the World Health Organization (WHO) defines diarrhea as three or more loose or liquid stools per 24 hours, the definition in pediatric trials ranges from one to three abnormally loose stools per 24 to 48 hours ([Johnston 2010](#)). Additionally, stool frequency is more difficult to quantify in diaper-aged children with diarrhea and may vary substantially between infants and older children.

PROBIOTICS

Probiotics refer to so-called "friendly" non-pathogenic bacterial or yeast microbiota intended to benefit the host via altering the microflora by implantation or colonization ([Schrezenmeir 2001](#)). The rationale behind probiotic administration is based on re-inoculation and normalization of unbalanced indigenous microflora using specific probiotic strains. Probiotics have been administered both prophylactically and therapeutically in an attempt to modify the mucosal, epithelial, intestinal and systemic immune activity in ways that may benefit human health. Probiotics are reported to improve microbial balance in the intestinal tract and display both antibacterial and immune regulatory effects in humans ([Gibson 1998](#); [Goldin 1998](#)). Probiotics commonly administered in randomized controlled trials of AAD are: *Lactobacillus acidophilus*, *Lactobacillus bulgaris*, *Lactobacillus casei*, *Lactobacillus rhamnosus*, *Bifidobacteria bifidum*, *Bifidobacteria longum*, *Streptococcus thermophilus*, *Saccharomyces boulardii* and *Clostridium butyricum*.

PREVIOUS REVIEWS ON PROBIOTICS AND AAD

Four meta-analyses have addressed the use of probiotics, alone or in combination, for the prevention of AAD in the general population. The results favoured probiotic co-administration with antibiotics (RR 0.43; 95% CI 0.31 to 0.58; [McFarland 2006](#); RR 0.48; 95% CI 0.35 to 0.65; [Sazawal 2006](#); RR 0.40; 95% CI 0.28 to 0.57; [Cremonini 2002](#) and OR 0.37; 95% CI 0.26 to 0.53; [D'Souza 2002](#)). Additionally, meta-analyses addressing the use of a single probiotic agent to prevent AAD examining *Saccharomyces boulardii* (*S. boulardii*) and *Lactobacillus* have also favoured probiotic treatment (RR 0.35, 95% CI 0.19 to 0.67; [Kale-Pradhan 2010](#); RR 0.47, 95% CI: 0.35 to 0.63; [McFarland 2010](#); and RR 0.43; 95% CI: 0.23 to 0.78; [Szajewska 2005](#)). Three meta-analyses of randomized trials to evaluate the efficacy of probiotics for preventing antibiotic-induced diarrhea in children have also suggested benefit (RR 0.43; 95% CI 0.25 to 0.75; [Johnston 2006](#); RR 0.44; 95% CI 0.25 to 0.77; [Szajewska 2006](#); and RR 0.43, 95% CI 0.25 to 0.75; [Johnston 2007](#)), the latter of which this review aims to update.

SAFETY OF PROBIOTICS

According to the best available evidence, the safety of diverse probiotic interventions does not appear to be a concern in healthy individuals ([Whelan 2010](#); [Johnston 2007](#); [Hammerman 2006](#); [Borriello 2003](#)). Infections (e.g. bacteremia, endocarditis, septicemia, pneumonia, deep abdominal abscesses) resulting from probiotic use have been reported in neonates, severely debilitated and immuno-compromised individuals ([Land 2005](#); [Salminen 2004](#); [Mackay 1999](#); [Piarroux 1999](#); [Rautio 1999](#); [McFarland 1998](#); [Salminen 1998](#); [Saxelin 1996](#); [Hata 1988](#); [Sussman 1986](#)), and there is still debate on the safety of probiotics in these patients. Nevertheless, prospective studies have demonstrated the safety of probiotics in immuno-compromised adults and children with HIV and preterm neonates, with no infections secondary to probiotics reported ([Bin-Nun 2005](#); [Lin 2005](#); [Salminen 2004](#); [Cunningham-Rundles 2000](#)).

Two recent systematic reviews have addressed the safety of *Saccharomyces boulardii* (*S. boulardii*) and other probiotics ([McFarland 2010](#); [Whelan 2010](#)). The first, a systematic review of randomized controlled trials (RCTs), reports on a wide diversity of adult patients randomized to *S. boulardii* as part of a clinical trial (traveller's diarrhea, n = 1596; AAD, n = 958; acute diarrhea, n = 156; enteral tube feeding, n = 103; IBD, n = 66; IBS, n = 16, HIV-related diarrhea, n = 18 and giardia infections, n = 50). These studies provide safety data for a total of 2963 adult patients. The only adverse reactions associated with *S. boulardii* were thirst (n = 5 patients) and constipation (n = 8 patients) in a trial of patients with *C. difficile* infections ([McFarland 1998](#)). No case of *S. boulardii* fungemia has been reported in these diverse patient populations ([McFarland 2010](#)).

A systematic review of case reports, randomized and non-randomized trials of probiotic safety in patients receiving nutritional support included 53 trials involving 4131 patients receiving probiotics. Most trials demonstrated either no effect or a positive effect on outcomes related to safety (e.g. infections, mortality). Three trials reported increased complications, which were largely noninfectious in nature and specific to patients with pancreatitis or undergoing transplant ([Whelan 2010](#)). The systematic review also reported 20 case reports of adverse events in 32 patients, 27 of which were infections due to *S. boulardii* (strain unspecified) or *Lactobacillus rhamnosus* GG (n = 5). Of the 32 patients having been administered *S. boulardii* with subsequent infections (i.e. fungemia, bacteremia), 11 of these were in children (either preterm neonates, severely debilitated or immuno-compromised children with underlying risk factors including central venous catheter use and disorders associated with bacterial/fungal translocation). Each of the children recovered after *S. boulardii* or *Lactobacillus* GG was discontinued, removing the central venous catheter (n = 7) and an antibiotic or anti-fungal was administered (n = 11). The authors of the study reported that these case reports likely reflect the wide use of *S. boulardii* and *Lactobacillus* GG in clinical settings, rather than their increased virulence ([Whelan 2010](#)).

AIMS OF TREATMENT

The aim of treatment with probiotics is to prevent or ameliorate diarrhea (i.e., shorten duration and/or severity of diarrhea).

OBJECTIVES

PRIMARY

- 1) To systematically assess whether probiotics (any specified strain or dose) co-administered with antibiotics (any agent) reduce the incidence of antibiotic-associated diarrhea in children.
- 2) To systematically assess adverse events of probiotics when co-administered with antibiotics in children.

SECONDARY

- 1) To systematically assess which probiotic strain(s) and dose(s) yield the most beneficial results in reducing the incidence of diarrhea.
- 2) To systematically assess whether probiotics (any specified strain or dose) co-administered with antibiotics (any agent) reduce the duration of diarrhea.
- 3) To systematically assess whether probiotics (any specified strain or dose) co-administered with antibiotics (any agent) reduce the daily stool frequency.

METHODS OF THE REVIEW

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

All randomized controlled trials irrespective of language or publication status, in which a specified probiotic agent has been compared to placebo, active, or no treatment control were considered for inclusion.

Types of participants

Children (0 to 18 years of age), male or female of any ethnic group being administered antibiotic therapy for any reason were considered for inclusion.

Types of intervention

Intervention group: specific, identified probiotic in any form (e.g. capsule, sachet, yogurt). Trials investigating non-specific probiotic or yogurt agents (e.g. products that do not label the probiotic strain and dose) were not considered. Trials combining probiotics with prebiotics were included if the prebiotic dose was less than 2.5 grams, as this was judged to be of limited impact to alter the gut milieu ([Davis 2010](#) ; [Gibson 2004](#) ; [Roberfroid 1998](#)). Control group: placebo, active, or no treatment control. All studies comparing probiotics to conventional care (i.e. diosmectite, loperamide) or probiotics plus conventional care versus conventional care plus placebo or no treatment were considered for the review.

Types of outcome measures

PRIMARY OUTCOMES

1. Incidence of diarrhea using the primary investigators' definition (i.e. frequency, consistency of bowel movements)
2. Number and type of adverse events (e.g. bacteremia, meningitis)

SECONDARY OUTCOMES

1. Mean duration of diarrhea
2. Mean stool frequency

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

Search methods for identification of studies

In May 2010, a comprehensive search of the following relevant databases irrespective of publication status or language was conducted: The Cochrane Central Register of Controlled Trials (CENTRAL) on the Cochrane Library (2010 Issue 2), the trial registers of the Cochrane IBD/FBD Review Group, the Cochrane Complementary Medicine Field's Register of Controlled Trials, MEDLINE (1966 to 2010), EMBASE (1980 to 2010), CINAHL (1982 to 2010), AMED (1985 to 2010), Web of Science (1945 to 2010).

HANDSEARCHES

Bibliographies of randomised controlled trials and review articles were checked for additional studies not identified by the electronic searches.

ADDITIONAL SEARCHES

We searched the International Bibliographic Information on Dietary Supplements (IBIDS) as well as ongoing trials through ClinicalTrials.gov and Current Controlled Trial Register, which houses the NHS Controlled Trials Register, the National Institute of Health Register, the National Research Register, and the International Standard Randomized Controlled Trial Number Register.

The MEDLINE search strategy was as follows:

1. exp PROBIOTICS/tu or probiotic\$.tw., 2. exp LACTOBACILLUS/ or lactobacill\$.tw. or "l acidophilus".tw. or "l casei".tw. or bifidobacter\$.mp. or "b infantis".tw. or "b bifidum".tw. or "b longum".tw. or saccharomyce\$.mp. or "s boulardii".tw. or clostridium butyricum.tw. or clostridium difficile.mn. or "strentococcus thermophilus".tw. or enterococcus faecium.mn. 3.

exp antibiotic\$ or biotherapeutic agent\$.tw., 4. or/1-3, 5. exp Anti-Bacterial Agents/ or antimicrobial\$.tw. or antibiotic\$.tw., 6. ((antimicrobial or anti microbial or antimicrobial or antimycobacteri\$ or antibacteri\$ or bacteriocid\$) adj3 agent\$).tw., 7. 5 or 6, 8. exp DIARRHEA/ or diarrhea.tw. or diarrhoe\$.tw. or diarhe\$.tw. or diahoe\$.tw. or dysenter\$.tw. or gastro enteritis\$.tw. or gastroenteriti\$.tw., 9. and/4,7-8, 10. child/ or infant/ or adolescence/ or exp infant, new born/ or exp child, preschool/, 11. (child\$ or newborn\$ or adolescen\$ or infan\$).tw., 12. (preschool\$ or pre-school\$).tw., 13. teen\$.tw. 14., (kindergarten\$ or kindergarden\$).tw., 15. elementary school\$.tw., 16. secondary school\$.tw., 17. nursery school\$.tw., 18. high school\$.tw., 19. highschool\$.tw., 20. youth\$.tw., 21. (baby\$ or babies\$ or premie\$ or premature\$).tw., 22. (schoolchild\$ or "school child\$").tw., 23. (schoolage\$ or school age\$).tw., 24. toddler\$.tw., 25. pubert\$.tw., 26. (pre-pubescent\$ or prepubescen\$ or post-pubescent\$ or postpubescen\$).tw., 27. (kid or kids or boy\$ or girl\$).tw., 28. juvenile.tw., 29. or/10-28, 30. 9 and 29, 31. Cochrane RCT filter (Dickersin 1994). 32. 30 and 31[/=MeSH term, exp=explode, tw=text word, mp=multipurpose word, \$=truncation]

DATA COLLECTION AND ANALYSIS

Data collection and analysis

The screening, selection, data extraction and risk of bias assessment were done independently and in duplicate by two investigators.

STUDY SELECTION

Search results were screened using titles of papers, and when available, abstracts. The full-text of the selected articles was retrieved and assessed for inclusion according to pre-specified selection criteria. Inter-rater reliability was measured using kappa statistics and disagreement was resolved by discussion.

DATA EXTRACTION

Using a standardized data extraction form we extracted the following data: author, year of publication, language, study setting, funding source, definition and diagnostic criteria for diarrhea, inclusion and exclusion criteria for participants, patient characteristics (age, gender, diagnosis, socioeconomic status), number of patients allocated to each group, presence/absence of intention to treat analysis (whether patients for whom data were available were analyzed as randomized), participants lost to follow-up (LTFU), if so, reasons for LTFU described and information about methods of imputation, measures of compliance, specified antibiotic, specified probiotic, duration, dosage and schedule of antibiotic, duration, dosage and schedule of probiotic, and outcome measures (incidence of diarrhea, number of adverse events, mean duration of diarrhea, mean stool consistency, and mean stool frequency).

QUALITY ASSESSMENTS

Quality components for each included RCT were assessed for selection, detection, performance, reporting and loss to follow-up bias. Each of the included studies was evaluated using the risk of bias instrument to assess sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other sources of bias ([Hartling 2009](#)).

We also employed the GRADE system for rating overall quality of evidence for each of the outcomes. In particular, randomized trials begin as high quality evidence, but may be rated down by one or more of five categories of limitations: (1) risk of bias, (2) consistency, (3) directness, (4) imprecision, and (5) reporting bias. The quality of evidence for each main outcome can be determined after considering each of these elements, and categorized as either 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, but there is a possibility that it is substantially different); low (our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect); 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) ([Guyatt 2008](#)).

STATISTICAL ANALYSIS

Results were combined unless diversity (clinical and/or statistical heterogeneity) suggested combination was unreasonable. Dichotomous data are presented as relative risks, and continuous data as weighted mean differences, along with their corresponding 95% confidence intervals. Using control event risks from the included trials, the number needed to treat (NNT) or the number needed to harm (NNH) was calculated for statistically significant dichotomous outcomes. Adverse events were summarized using risk difference since these events were rare. Random-effects models were used and fixed-effect models were considered in sensitivity analyses. Heterogeneity was investigated using the I² statistic ([Higgins 2003](#)). Meta-regression or the Chi² test for heterogeneity - depending on the number of trials included - were used to address a priori hypotheses explaining heterogeneity. To explore possible explanations for heterogeneity, subgroup analyses were subdivided by: probiotic strain(s) (when two or more trials administered the same strains), antibiotics that are specific to anaerobes (most associated with diarrhea adverse events), diagnostic criteria for diarrhea (e.g. ≥ 3 watery/liquid stools per day for 2 consecutive days versus ≥ 3 watery/liquid stools per day), dosage of probiotic (≥ 5 billion colony forming units of live bacteria/yeast, < 5 billion colony forming units of live bacteria/yeast) and quality criterion (e.g. risk of bias instrument). To assess the potential influence of missing responses (e.g. children lost to follow up) sensitivity analyses were applied for the primary outcome, incidence of diarrhea. Although many approaches exist for evaluating the sensitivity of results to missing responses ([Akl 2009](#); [Hollis 1999](#)), we elected to make assumptions about the missing data which were extreme but still plausible (i.e. 60% of children loss to follow-up in probiotic group and 20% loss to follow-up in the control group had diarrhea). To evaluate the potential for publication bias, funnel plots, the rank correlation test ([Begg 1994](#)) and weighted regression ([Egger 1997](#)) were applied to the main efficacy outcome, incidence of diarrhea. If publication bias was apparent, adjustment of the pooled estimates was considered using the trim and fill method ([Duval 2001](#)). More than one method to evaluate publication bias was considered since the relative merits of the methods are not

well established.

METHODOLOGICAL QUALITY

RESULTS

Results

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#).

A previous literature search conducted in August 2006 identified 10 relevant studies for inclusion (7 English, 2 Italian, 1 French) and is described in detail elsewhere ([Johnston 2007](#)). An updated search was conducted in May 2010 (search dates: January 2005 to May 25, 2010). A total of 416 studies were identified from the primary electronic databases (Medline 144, EMBASE 92, CENTRAL 41, CINAHL 41, Web of Science 98, AMED 0). Of these 173 were identified as duplicates, leaving 243 abstracts and/or titles identified as original publications. A grey literature search (Clinicaltrials.gov, NHS Evidence, IBIDS) identified 1 additional relevant study for full-text review. Independent review (BCJ, JZG) of these titles and/or abstracts identified 14 potentially relevant studies for full-text review. Two authors (JZG, XS) independently assessed these studies and identified six that met the inclusion criteria. The inter-rater proportion of overall agreement on inclusion and exclusion was 93% with a kappa coefficient of 0.85 (95% CI 0.57 to 1.00). Reasons for exclusion were as follows: five studies did not include children ([Kim 2008](#); [Koning 2008](#); [Wenus 2008](#); [Beausoleil 2007](#); [Can 2006](#)); one study used a gastro-intestinal symptoms rating scale that, while inclusive of stool frequency and consistency, did not report data specific to those outcomes ([Lionetti 2006](#)); one study involved *Sacchomyces boulardii* for pediatric infectious diarrhea (i.e., amebiasis-associated diarrhea) ([Savas-Erdeve 2009](#)); and one study did not administer probiotics concurrently with antibiotics ([Honeycutt 2007](#)). A detailed summary of all included and excluded studies can be found in the "Characteristics of Included Studies" and "Characteristics of Excluded Studies" tables.

Design

All included studies were prospective, randomized, controlled trials (placebo, active or no treatment control arm).

Patient population

For the purposes of this systematic review LTFU can be understood as incomplete ascertainment of the primary outcome for some participants in an RCT. Patients for whom data were not available for the primary outcome were classified as LTFU. After accounting for LTFU the 16 studies included a total of 2941 patients (1516 treatment, 1425 controls). Patients were diagnosed with upper and lower respiratory tract, ear, gastrointestinal, dermatological, or other infections ([Merenstein 2009](#); [Szajewska 2009](#); [Ruszczynski 2008](#); [Szymanski 2008](#); [Kotowska 2005](#); [LaRosa 2003](#); [Arvola 1999](#); [Benhamou 1999](#); [Vanderhoof 1999](#); [Contardi 1991](#); [Tankanow 1990](#); [Destura unpublished](#)), and meningitis or septicemia ([Jirapinyo 2002](#)). In one study the type of infection that necessitated antibiotic therapy was not reported ([Conway 2007](#)). The health care setting was reported in 14 studies and consisted of: private primary care practices ([Merenstein 2009](#); [Conway 2007](#); [Benhamou 1999](#); [Vanderhoof 1999](#); [Contardi 1991](#); [Tankanow 1990](#)), hospitalized inpatients ([Szajewska 2009](#); [Correa 2005](#); [Jirapinyo 2002](#)), an outpatient university teaching hospital ([Kotowska 2005](#); [Arvola 1999](#)), and both inpatient and outpatient hospital populations ([Destura unpublished](#)). In addition to inpatient and outpatient hospital populations, [Ruszczynski 2008](#) also enrolled from a private practice, and [Szymanski 2008](#) also enrolled from outpatient clinics. Children enrolled were from families of diverse socioeconomic status, including developed and developing countries such as Brazil ([Correa 2005](#)), the Philippines ([Destura unpublished](#)), Poland ([Szajewska 2009](#); [Ruszczynski 2008](#); [Szymanski 2008](#)), Thailand ([Jirapinyo 2002](#)) and Turkey ([Erdeve 2004](#)). Children ranged from 1 month to 18 years of age. Eleven studies provided information regarding the participants' mean age: 4.5 years ([Arvola 1999](#)), 2.4 years ([Benhamou 1999](#)), 1.8 years ([Correa 2005](#)), treatment 4.1 years and control 4 years ([Destura unpublished](#)), 4.8 years ([Kotowska 2005](#)), 6.6 years ([LaRosa 2003](#)), 2.9 years treatment and 3.2 years control ([Merenstein 2009](#)), treatment 4.6 years and control 4.5 years ([Ruszczynski 2008](#)), 12.3 years treatment and 11.9 years control ([Szajewska 2009](#)), 2.5 years ([Tankanow 1990](#)) and 4 years ([Vanderhoof 1999](#)). Two studies provided only the age range of enrolled participants: 8 months to 3 years ([Contardi 1991](#)) and 1 month to 3 years ([Jirapinyo 2002](#)). One study provided median age with a range: 7 years (range 1 to 15) ([Szymanski 2008](#)). Eleven studies included both males and females (838 males and 821 females), and five studies did not state sufficient information regarding gender ([Conway 2007](#); [Erdeve 2004](#); [Jirapinyo 2002](#); [Arvola 1999](#); [Benhamou 1999](#)).

Interventions

Overall the trials provided between 3 and 30 days of antibiotic therapy. Most trials provided oral antibiotics. Three trials administered intravenous antibiotics to some patients (e.g., cefuroxime): 60/246 (24.3%) ([Kotowska 2005](#)); 87/240 (36.3%) ([Ruszczynski 2008](#)); 6/78 (7.7%) ([Szymanski 2008](#)). [Ruszczynski 2008](#) also provided intravenous (IV) antibiotics followed by oral antibiotics (17/240; 7.1%) and intramuscular (IM) antibiotics (2/240; 0.8%). In three trials it was unclear what antibiotics and/or route was used ([Merenstein 2009](#); [Conway 2007](#); [Destura unpublished](#)). Two studies provided oral amoxicillin alone ([Contardi 1991](#); [Tankanow 1990](#)) using a standard pediatric dosage range (20 to 50 mg/kg/day), whereas the remaining trials provided a mixture of oral antibiotic agents including: bactericidal cephalosporins (e.g., cefotaxime, cefprozil), bacteriostatic macrolides (e.g., clarithromycin, erythromycin), and the bactericidal beta-lactams/penicillins. In particular, nine studies described the antibiotic classes administered. Four studies administered a host of cephalosporins (n = 341) and beta-lactams/penicillins (n = 931) ([Correa 2005](#); [Kotowska 2005](#); [Benhamou 1999](#); [Destura unpublished](#)), one study provided cephalosporins (n = 49), beta-lactams/penicillins in the form of amoxicillin-clavulanate (n = 36) and macrolides in the form of erythromycin (n = 34) ([LaRosa 2003](#)), and one study provided beta-

lactams/penicillins in the form of sulbactam-ampicillin (n = 234) and macrolides in the form of azithromycin (n = 232) ([Erdeve 2004](#)). One study provided all participants (n = 83) with three concurrent pharmaceuticals: amoxicillin, clarithromycin, and omeprazole ([Szajewska 2009](#)). [Szymanski 2008](#) provided cephalosporins (n = 20); beta-lactams/penicillins in the forms of penicillin, amoxicillin, or amoxicillin+clavulanate (n = 39); macrolides (n = 18); and aminoglycosides (n = 1). [Ruszczynski 2008](#) provided cephalosporins (n = 89); beta-lactams/penicillins in the forms of penicillin, ampicillin, amoxicillin, or amoxicillin+clavulanate (n = 134); macrolides (n = 15); and clindamycin (n = 2).

Trials included treatment with either *Bacillus* spp., *Bifidobacterium* spp., *Lactobacilli* spp., *Lactococcus* spp., *Leuconostoc cremoris*, *Saccharomyces* spp., or *Streptococcus* spp. The strain(s) and daily dosage of the probiotic interventions included: *Lactobacillus* GG, 1 billion colony forming units (CFU) bacteria/day ([Szajewska 2009](#)); *Lactobacillus* GG, 20 to 40 billion CFU bacteria per day ([Arvola 1999](#)); *Lactobacillus* GG and inulin (a prebiotic), 10 to 20 billion CFU bacteria/day equalling 100 mg and 225 mg of the prebiotic inulin/day (the only study to use a weight-based approach) ([Vanderhoof 1999](#)); *Saccharomyces boulardii*, 4.5 billion yeast/day ([Benhamou 1999](#)); *Lactobacillus acidophilus* and *Bifidobacterium bifidus*, 3 billion CFU bacteria/day ([Contardi 1991](#)); *Bifidobacterium lactis* and *Streptococcus thermophilus*, 825 million CFU bacteria/day ([Correa 2005](#)); *Bacillus clausii*, 4 billion CFU bacteria/day ([Destura unpublished](#)); *Saccharomyces boulardii*, 5 billion CFU yeast/day ([Erdeve 2004](#)); *Lactobacillus acidophilus* and *Bifidobacterium infantis*, dose not reported ([Jirapinyo 2002](#)); *Saccharomyces boulardii*, 10 billion CFU of yeast/day ([Kotowska 2005](#)); *Lactobacillus sporogenes* and fructo-oligosaccharide (a prebiotic); 5.5 billion CFU bacteria/day and 250 mg prebiotic/day ([LaRosa 2003](#)); *Lactococcus lactis*, *L. plantarum*, *L. rhamnosus*, *L. casei*, *L. lactis* subspecies diacetylactis, *Leuconostoc cremoris*, *Bifidobacterium longum*, *B. breve*, *Lactobacillus acidophilus*, and *Saccharomyces florentinus*, at least half of a 150 ml drink containing 7 to 10 billion CFU bacteria and yeast/day ([Merenstein 2009](#)); *Lactobacillus rhamnosus*, 40 billion CFU bacteria/day ([Ruszczynski 2008](#)); *Bifidobacterium longum* PL03, *Lactobacillus rhamnosus* KL53A, and *Lactobacillus plantarum* PL02, 200 million CFU bacteria/day ([Szymanski 2008](#)); *Lactobacillus acidophilus* and *Lactobacillus bulgaricus*, 2 billion CFU bacteria/day ([Tankanow 1990](#)); and finally *Streptococcus thermophilus*, *Lactobacillus acidophilus*, and *Bifidobacterium animalis* subsp. *lactus* or *Streptococcus thermophilus* and *Lactobacillus delbrueckii* subsp. *bulgaris*, 1 billion CFU bacteria/day ([Conway 2007](#)).

Comparison

In 10 studies, the probiotic(s) intervention was compared to a placebo control group, two trials compared probiotics to conventional care including formula and diosmectite ([Correa 2005](#); [Benhamou 1999](#)), two trials compared probiotics to no treatment ([Erdeve 2004](#); [Destura unpublished](#)), one trial compared a live probiotic drink to a heat-killed probiotics drink ([Merenstein 2009](#)), and one trial used three arms: 'bioyogurt,' commercial yogurt, and no yogurt ([Conway 2007](#)). In order to avoid unit of analysis errors, for the purposes of this review we grouped the two yogurt arms of the latter trial together. In one placebo-controlled trial, contact with authors revealed that the placebo contained an inert amount of inulin (325 mg) - a prebiotic used as capsule filler ([Vanderhoof 1999](#)). Five additional placebo-controlled trials provided information on the choice of comparison stating that the placebos contained maltodextrine, non-fat milk and saccharose, *saccharum lactis*, 'sugar', and 'lactose' respectively ([Szajewska 2009](#); [Ruszczynski 2008](#); [Kotowska 2005](#); [Jirapinyo 2002](#); [Tankanow 1990](#)). For the two trials involving active controls with conventional care, one trial administered diosmectite (an antidiarrheal gastrointestinal protectant drug) ([Benhamou 1999](#)) and the second administered formula containing vitamins, minerals and protein ([Correa 2005](#)).

Outcomes

Fifteen studies (n = 2882) provided data on the incidence of diarrhea, 11 studies (n = 1583) reported on adverse events, five studies (n = 897) reported mean duration of diarrhea, and four studies (n = 425) reported mean stool frequency. The criteria for defining the incidence of diarrhea varied among the studies and ranged from clinical determination of diarrheal incidence ([Merenstein 2009](#)); one or more abnormally loose bowel movements per day ([Tankanow 1990](#)); two or more liquid stools per day on at least two occasions during the course of the study ([Vanderhoof 1999](#)); three or more liquid/watery stools per day ([Erdeve 2004](#); [Benhamou 1999](#)), three or more watery/loose/liquid stools per day for two consecutive days ([Conway 2007](#); [Correa 2005](#); [Kotowska 2005](#); [Arvola 1999](#)); change in bowel habits with the passage of three or more liquid stools per day for at least 2 consecutive days 48 hours after initiation of antibiotic therapy ([Destura unpublished](#)); to greater than or equal to 3 loose or watery stools per day for a minimum of 48 hrs, occurring during and/or up to 2 weeks after the end of the antibiotic therapy ([Szajewska 2009](#); [Ruszczynski 2008](#); [Szymanski 2008](#)).

Three studies reported on viral and bacterial analysis of fecal samples ([Kotowska 2005](#); [Arvola 1999](#); [Destura unpublished](#)). Along with viral and bacterial fecal analysis, one trial reported on the metabolic activity of gut microflora: fecal urease, β -glucosidase and β -glucuronidase activity ([Arvola 1999](#)). Two trials reported on frequencies of retroviral diarrhea, salmonella diarrhea, shigella diarrhea and *C. difficile* diarrhea ([Ruszczynski 2008](#); [Kotowska 2005](#)). Other outcomes of potential interest included mean diarrhea incubation and percentage suffering from dehydration reported in one study ([Correa 2005](#)), fecal lactoferrin ([Destura unpublished](#)), and the need for IV rehydration, hospitalization of outpatients, and/or discontinuation of antibiotic treatment ([Ruszczynski 2008](#); [Szymanski 2008](#)). Additionally, one study reported on *H. pylori* outcomes such as positive rapid urea test, positive histopathology for *H. pylori*, and positive C13 urea breath test ([Szajewska 2009](#)). No studies reported on cost-effectiveness related to absenteeism from the workplace, daycare or school between treatment and control groups.

Risk of bias in included studies

Five studies reported information concerning a priori sample size calculations ([Merenstein 2009](#); [Ruszczynski 2008](#); [Conway 2007](#); [Kotowska 2005](#); [Vanderhoof 1999](#)). Loss to follow-up was substantial (i.e. > 20%) in 5/15 trials reporting the incidence of diarrhea ([Szajewska 2009](#); [Erdeve 2004](#); [Arvola 1999](#); [Benhamou 1999](#); [Tankanow 1990](#)). In particular, LTFU was 37% in [Tankanow 1990](#) and 29% in [Arvola 1999](#). Six trials provided a flow diagram to track participants some of which included details regarding drop-outs ([Merenstein 2009](#); [Szajewska 2009](#); [Ruszczynski 2008](#); [Szymanski 2008](#); [Conway 2007](#); [Kotowska 2005](#)). All studies were randomized parallel group designs. Fourteen studies

[Szymanski 2008](#); [Conway 2007](#); [Kotowska 2005](#)). All studies were randomized parallel group designs. Fourteen studies reported using a "double-blind" procedure. However, the risk of bias assessment determined that patients in the [Conway 2007](#) and [Tankanow 1990](#) studies were likely unblinded during treatment. Two trials were open label ([Contardi 1991](#); [Destura unpublished](#)). The validated risk of bias instrument categorizes risk into three categories: high risk of bias, low risk of bias and unclear. Eight trials were categorized as low risk ([Merenstein 2009](#); [Szajewska 2009](#); [Ruszczynski 2008](#); [Szymanski 2008](#); [Correa 2005](#); [Kotowska 2005](#); [LaRosa 2003](#); [Vanderhoof 1999](#)) and eight trials were categorized as high risk ([Erdeve 2004](#); [Jirapinyo 2002](#); [Arvola 1999](#); [Benhamou 1999](#); [Contardi 1991](#); [Tankanow 1990](#); [Destura unpublished](#); [Conway 2007](#)). See and for the overall results of the risk of bias assessment. The chance-adjusted agreement between reviewers on the application of risk of bias criteria was very good (kappa 0.77; 95% CI 0.50 to 1.03).

Effects of interventions

See: [Summary of findings for the main comparison Probiotics as an adjunct to antibiotics for the prevention of pediatric antibiotic-associated diarrhea in children](#)

Incidence of diarrhea

To allow for a heterogeneous definition of diarrhea, data (as a binary outcome) were included based on the primary authors' definition of the presence/absence of diarrhea. Fifteen studies (n = 2882) reported incidence of diarrhea. Using an available case (i.e. patients who did not complete the studies were not included in the analysis) approach as the primary analysis, four placebo-controlled studies showed a statistically significant reduction in the incidence of AAD (P < 0.05) ([Ruszczynski 2008](#); [Kotowska 2005](#); [LaRosa 2003](#); [Vanderhoof 1999](#)); one active-controlled study (formula) was statistically significant ([Correa 2005](#)), and one 'no treatment-control' study demonstrated statistical significance ([Erdeve 2004](#)). Six placebo-controlled studies ([Merenstein 2009](#); [Szajewska 2009](#); [Szymanski 2008](#); [Jirapinyo 2002](#); [Arvola 1999](#); [Tankanow 1990](#)), two no treatment-control studies ([Conway 2007](#); [Destura unpublished](#)), and one active-control (diosmectite) study ([Benhamou 1999](#)) did not show a statistically significant difference, but seven of these nine trials showed a non-significant trend favouring probiotics. The overall pooled results using an available case analysis showed that the use of probiotics produced a statistically significant reduction in the incidence of AAD. The incidence of AAD in the probiotic group was 9% compared to 18% in the active, placebo or no treatment control group (2874 participants; RR 0.52; 95% CI 0.38 to 0.72; random-effects). However, statistically significant heterogeneity was detected (P = 0.004) and this was moderate with respect to percent variability due to between (or inter-) study variability (I² = 56%) ([Higgins 2003](#)).

Adverse events

None of the studies specifically defined adverse events a priori. Three trials reported no adverse events ([Kotowska 2005](#); [Jirapinyo 2002](#); [Vanderhoof 1999](#)). Four trials reported adverse events ([Merenstein 2009](#); [Szajewska 2009](#); [Correa 2005](#); [Tankanow 1990](#)). [Tankanow 1990](#) reported 14 adverse events including rash, gas, vomiting, increased phlegm and chest pain. However, for each of the 14 events it was not clear in which group (treatment or control) the adverse events occurred. It appears that the 14 adverse events occurred in three participants ([Tankanow 1990](#)). It was assumed for the meta-analysis that the adverse events were in the treatment group. [Correa 2005](#) reported five participants with adverse events in the treatment group. These adverse events were related to the tolerability of the formula supplemented with probiotics. [Merenstein 2009](#) reported a case of emesis in the treatment group and a case of constipation in the control group. [Szajewska 2009](#) reported 18 adverse events in the treatment group and 13 in the control group. In both groups adverse events included nausea, vomiting, constipation, flatulence, taste disturbance, and low appetite. No statistically significant difference in adverse events was found between groups. Meta-analysis of all trials that included adverse events demonstrated no statistically significant differences in the incidence of adverse events (RD 0.00; 95% CI -0.01 to 0.02).

Mean duration of diarrhea

Five studies recorded the mean duration of diarrhea ([Correa 2005](#); [LaRosa 2003](#); [Arvola 1999](#); [Vanderhoof 1999](#); [Destura unpublished](#)). The standard deviation (SD) for one of the trials was not reported and this information was requested from authors with no response ([Vanderhoof 1999](#)). The SD was imputed for [Vanderhoof 1999](#) from a study reporting a similar mean duration of diarrhea for treatment and control ([Arvola 1999](#)). A post hoc sensitivity analysis was conducted to test the robustness of the mean duration results both before and after imputing data. The WMD was not statistically significant before including [Vanderhoof 1999](#) (WMD -0.42; 95% CI -1.01 to 0.16), although it was statistically significant after imputing the SD data (WMD -0.60; 95% -1.18 to -0.02). Statistically significant heterogeneity was detected (P = 0.008) and this was high with respect to percent variability due to between (or inter-) study variability (I² = 79%) ([Higgins 2003](#)).

Mean stool frequency

Four RCTs reported mean stool frequency ([Szymanski 2008](#); [Arvola 1999](#); [Vanderhoof 1999](#); [Contardi 1991](#)). SD data were imputed for one study ([Arvola 1999](#)). This study reported a range for the mean stool frequency for both treatment and control which was used to impute a SD for each study arm. A post hoc sensitivity analysis was conducted to test the robustness of the mean stool frequency results both before and after imputing data. The WMD excluding [Arvola 1999](#) was -0.36 (95% CI -0.70 to -0.02). After imputing SD data the WMD was not statistically significant -0.30 (95% CI -0.60 to -0.00; I² = 78%).

A PRIORI SUBGROUPS

Probiotic species

Four of 15 trials administered *Lactobacillus rhamnosus* species (three using strain *Lactobacillus* GG: [Szajewska 2009](#); [Arvola 1999](#); [Vanderhoof 1999](#); and one using strains E/N, Oxy, and Pen: [Ruszczynski 2008](#)), while three studied the yeast *Saccharomyces boulardii* (strain Iyo) ([Kotowska 2005](#); [Erdeve 2004](#); [Benhamou 1999](#)). Combined results from four *L. rhamnosus* studies (n = 611) were statistically significant indicating a protective effect (RR 0.35; 95% CI 0.22 to 0.56; I² = 0%). The summary statistic for the *Saccharomyces boulardii* trials (n = 1328) was not statistically significant (RR

0.45; 95% CI 0.14 to 1.48, I² = 88%). Tests for interaction revealed non-statistically significant species related heterogeneity.

Probiotic dose

The daily dosage of probiotic(s) varied greatly (200 million to 40 billion CFU/day). Fourteen of 15 studies that reported incidence of diarrhea data provided dosage information ([Merenstein 2009](#); [Szajewska 2009](#); [Ruszczynski 2008](#); [Szymanski 2008](#); [Conway 2007](#); [Correa 2005](#); [Kotowska 2005](#); [Erdeve 2004](#); [LaRosa 2003](#); [Arvola 1999](#); [Benhamou 1999](#); [Vanderhoof 1999](#); [Tankanow 1990](#); [Destura unpublished](#)). The a priori subgroup analyses on dose compared < 5 billion CFU/day versus ≥ 5 billion CFU/day. Seven studies providing children with 5 to 40 billion bacteria/yeast cells per day ([Merenstein 2009](#); [Ruszczynski 2008](#); [Kotowska 2005](#); [Erdeve 2004](#); [LaRosa 2003](#); [Arvola 1999](#); [Vanderhoof 1999](#)) showed evidence for the preventative effects of probiotics. For the high dose studies the pooled incidence of AAD in the probiotic group was 8% compared to 22% in the active, placebo or no treatment control group (RR 0.40; 95% CI 0.29 to 0.55; I² = 29%). Seven studies providing < 5 billion CFU bacteria/yeast per day: 200 million CFU/day ([Szymanski 2008](#)), 825 million CFU/day ([Correa 2005](#)), 1 billion CFU/day ([Conway 2007](#); [Szajewska 2009](#)), 2 billion CFU/day ([Tankanow 1990](#)), 4 billion CFU/day ([Destura unpublished](#)), and 4.5 billion CFU/day ([Benhamou 1999](#)) demonstrated non-significant results when combined. For the low dose studies the pooled incidence of AAD in the probiotic group was 8% compared to 11% in the active, placebo or no treatment control group (RR 0.80; 95% CI 0.53 to 1.21; I² = 36%). A test of interaction revealed statistically significant dose related heterogeneity (P = 0.010; I² = 85.1%). Using 11 criteria to evaluate the credibility of the subgroup analysis, the results indicate that the subgroup effect based on dose (≥ 5 billion CFU/day) was convincing ([Sun 2010](#); See [Appendix 1](#), Table 1).

Quality

Of the 15 studies reporting on incidence of diarrhea, eight were rated as having a low risk of bias ([Merenstein 2009](#); [Szajewska 2009](#); [Ruszczynski 2008](#); [Szymanski 2008](#); [Correa 2005](#); [Kotowska 2005](#); [LaRosa 2003](#); [Vanderhoof 1999](#)) and seven were rated as having a high risk of bias ([Conway 2007](#); [Erdeve 2004](#); [Jirapinyo 2002](#); [Arvola 1999](#); [Benhamou 1999](#); [Tankanow 1990](#); [Destura unpublished](#)). A subgroup analysis of those trials rated as a low risk of bias versus those rated as exhibiting a high risk of bias showed statistically significant results for the low risk studies (Low risk; RR 0.45; 95% CI 0.34 to 0.60 versus high risk RR 0.65; 95% CI 0.37 to 1.13 respectively). A test of interaction was not statistically significant (P = 0.26). Additionally, summary statistics from the subgroups for high risk of bias and low risk of bias did not exhibit an inverse trend between quality and therapeutic effect. In other words, as quality (e.g. randomization, blinding, allocation concealment) increased, the therapeutic effect of probiotics did not decrease.

Definition of diarrhea

The criteria for diarrhea varied amongst the studies with thirteen studies defining diarrhea onset/diagnosis. Eight studies ([Szajewska 2009](#); [Ruszczynski 2008](#); [Szymanski 2008](#); [Conway 2007](#); [Correa 2005](#); [Kotowska 2005](#); [Arvola 1999](#); [Destura unpublished](#)) defined diarrhea as ≥ 3 loose/watery/liquid stools per day for at least 2 consecutive days (RR 0.40; 95% CI 0.28 to 0.59). Two trials ([Erdeve 2004](#); [Benhamou 1999](#)) defined diarrhea as ≥ 3 watery/liquid stools per 24 hours (RR 0.65; 95% CI 0.15 to 2.85). [Tankanow 1990](#) defined diarrhea as one or more abnormally loose bowel movements per 24 hours (RR 0.96; 95% CI 0.61 to 1.50). [LaRosa 2003](#) defined diarrhea as at least two liquid bowel movements per 24 hour period (RR 0.47; 95% CI 0.29 to 0.77). [Vanderhoof 1999](#) defined diarrhea as two or more loose stools on two or more occasions throughout the study period (RR 0.29; 95% CI 0.13 to 0.63). A trend between the definition of diarrhea used in the included trials and efficacy was not found (i.e. increased probiotic efficacy in trials with more conservative definitions of AAD [i.e. one or more loose stools per day]).

Antibiotics

Six of 15 trials provided adequate details regarding the antibiotic agent (co-administered with probiotics) ([Ruszczynski 2008](#); [Correa 2005](#); [Kotowska 2005](#); [Erdeve 2004](#); [Benhamou 1999](#); [Destura unpublished](#)). Antibiotic agents were categorized into antibiotic class (e.g. beta-lactams/penicillins, cephalosporins, macrolides) and subgroup analysis was performed on 3/6 trials that administered ≥ 5 billion CFU/day ([Ruszczynski 2008](#); [Kotowska 2005](#); [Erdeve 2004](#)). In a subgroup of patients given beta-lactams/penicillins only, a statistically significant difference between probiotic treatment and control groups (RR 0.27; 95% CI 0.15 to 0.46) was observed ([Ruszczynski 2008](#); [Kotowska 2005](#); [Erdeve 2004](#)). Two trials reported AAD incidence rates in patients administered cephalosporins ([Ruszczynski 2008](#); [Kotowska 2005](#)) and two reported rates in patients administered macrolides ([Ruszczynski 2008](#); [Erdeve 2004](#)) both demonstrating a non-significant difference (RR 0.49; 95% CI 0.17 to 1.45; and RR 0.50; 95% CI 0.21 to 1.19) respectively. Tests for interaction (beta-lactams/penicillins versus cephalosporins; beta-lactams/penicillins versus macrolides) were not statistically significant (P = 0.33; and P = 0.24 respectively).

SENSITIVITY ANALYSES

Random- versus fixed-effect

A sensitivity analysis using random- (RR 0.52; 95% CI 0.38 to 0.72) versus fixed-effect models (RR 0.51; 95% CI 0.42 to 0.62) for the incidence of diarrhea, indicated limited differences between the relative risk and corresponding 95% confidence intervals. Nonetheless, because the I² statistic demonstrated moderate heterogeneity within and between studies, a random-effects model was used for all statistical analyses.

Imputation for missing data analysis

Incidence of diarrhea analysis

There were 3392 pediatric participants originally randomized in the 15 trials reporting on the primary outcome (incidence of diarrhea). Eleven of 15 trials reported LTFU of which five reported substantial attrition concerns. Loss to follow-up was 20%, 21%, 28%, 28% and 36% in the [Szajewska 2009](#); [Arvola 1999](#); [Benhamou 1999](#); [Erdeve 2004](#); and [Tankanow 1990](#) studies respectively. We elected to make assumptions about the missing data which were extreme but still plausible

for two separate analyses: i) involving the seven trials having employed high dose probiotics (≥ 5 billion CFU/day) for the primary efficacy analysis, and ii) involving all trials that reported on the primary efficacy analyses. Six of seven trials using ≥ 5 billion CFU/day had loss to follow-up (6 to 28%), whereas 11 of 15 reporting on the primary efficacy outcome had loss to follow-up. If no information on the number of patients randomized to each group, or the number LTFU from each group (e.g. not reported in the published trial or unsuccessful contact with authors) was available, it was assumed that the LTFU in the treatment and control groups were as even as possible (block randomization). After imputing data for the missing responses, an extreme-plausible intention to treat (ITT) analysis (60% of children loss to follow-up in probiotic group and 20% loss to follow-up in the control group had diarrhea) involving the seven high-dose trials showed a marginally significant benefit favouring probiotics. For the high dose studies the pooled incidence of AAD in the probiotic group was 17% compared to 22% in the active, placebo or no treatment control group (RR 0.72; 95% CI 0.53 to 0.99; I² = 57%). The extreme-plausible ITT analysis based on all 15 trials reporting probiotics for preventing the onset of diarrhea was not statistically significant. The pooled incidence of AAD in the probiotic group was 16% compared to 18% in the active, placebo or no treatment control group (RR 0.81; 95% CI 0.63 to 1.04, I² = 59%).

Adverse event analysis

Assuming that patients LTFU in each of the trials may have had adverse events, we conducted a sensitivity analysis to test the robustness of the primary available case analysis. To do so, we suspected that the most reasonable assumption to make for those who were LTFU was that LTFU had the same adverse event rate as those followed up in their respective randomization groups. In particular, among the four trials that did report adverse events, the proportion of adverse events was 14.4% (27/187) in the treatment group and 14/192 (7.29%) in the control group. For all eleven trials that reported LTFU, we assigned the same adverse event rate as those followed up in their respective randomization groups (14.4% and 7.29% assumed to have adverse events among treatment and control groups respectively) to those who were LTFU. Similar to our primary available case harms analysis (RD 0.00; 95% CI -0.01 to 0.02), the same event rate assumptions analysis which included all 16 trials yielded a pooled estimate of effect (RD 0.01; 95% CI -0.00 to 0.02).

Publication bias

A funnel plot analysis provides no compelling indication of publication bias showing general symmetry of the funnel for the relationship between risk ratio and standard error. (See). Although there are a limited number of trials reporting on the incidence of diarrhea (n = 15), additional tests based on Begg's test of correlation (P = 0.55) and Egger's regression test (P = 0.46), also failed to suggest evidence of publication bias. Although our tests for publication bias fail to demonstrate that negative studies remain unpublished, the literature suggests that these tests are, at best, subjective. The validity of these tests has not been established and as a result strong claims for or against publication bias should be avoided if there is not clear evidence suggesting the presence or absence of negative results remaining unpublished ([Ioannidis 2008](#); [Ioannidis 2007](#); [Lau 2006](#)).

DISCUSSION

Discussion

The primary objective of this review was to determine if the co-administration of probiotics with antibiotics prevents or ameliorates AAD in children. Sixteen eligible studies included treatment with *Bacillus* spp., *Bifidobacterium* spp., *Lactobacilli* spp., *Lactococcus* spp., *Leuconostoc cremoris*, *Saccharomyces* spp., or *Streptococcus* spp., alone or in combination. Seven of 16 trials tested *S. boulardii* or *Lactobacillus rhamnosus* spp. Available case (i.e. patients who did not complete the studies were not included in the analysis) results from 15/16 trials reporting on the incidence of diarrhea, demonstrated a relatively large, precise benefit from probiotics (RR 0.52; 95% CI 0.38 to 0.72, I² = 56%). An a priori hypothesis testing for heterogeneity indicated that high dose (≥ 5 billion CFUs/day; RR 0.40 95% CI 0.29 to 0.55; I² = 29%) is significantly more effective than low probiotic dose (< 5 billion CFUs/day; RR 0.80 95% CI 0.53 to 1.21). Based on high-dose probiotics, the number needed to treat (NNT) to prevent one case of diarrhea is seven (NNT 7; 95% CI 6 to 10).

To test the robustness of our available case analysis, we elected to make assumptions about the missing data from the trials having employed high dose probiotics (≥ 5 billion CFU/day) which were less extreme and arguably more plausible. Six of seven trials using ≥ 5 billion CFU/day had loss to follow-up (6 to 28%). After imputing data for the missing responses, an extreme-plausible ITT analysis (60% of children loss to follow-up in probiotic group and 20% loss to follow-up in the control group had diarrhea) indicated a marginally significant benefit for high dose probiotics (1776 participants; RR 0.72; 95% CI 0.53 to 0.99; I² = 57%). An extreme-plausible ITT analysis of the 15 trials reporting on the incidence of diarrhea was not statistically significant (RR 0.81; 95% CI 0.63 to 1.04; I² = 59%).

Statistical heterogeneity was moderate in both of the available case analyses. We specified a priori subgroup hypotheses to explore the heterogeneity in our results that included probiotic species, probiotic dose, risk of bias (e.g., blinding, allocation concealment), antibiotic agent and definition of diarrhea. A test for heterogeneity was significant for one subgroup - probiotic dose - providing evidence that a dose-response gradient is the most likely explanation for the observed statistical heterogeneity. The test for interaction for potential dose related heterogeneity was statistically significant (P = 0.010). Using 11 criteria to evaluate the credibility of the subgroup analysis, the results indicate that the subgroup effect based on dose (≥ 5 billion CFU/day) was convincing ([Sun 2010](#); See [Appendix 1](#), Table 1). This represents an important finding as dosage recommendations for products containing probiotics available in pharmacies and health food stores have a wide range (e.g. 1 to 450 billion CFU/day); and dosages approaching the lower range may not confer a therapeutic benefit ([Raza 1995](#)). Given our review included trials testing 10 different probiotics either alone or in combination, amongst a diverse clinical population, with nearly all demonstrating favourable results; for the purposes of clinical recommendations and future research, our findings suggest that the minimal effective dose may be 5 billion CFU/day.

Regarding safety. 11/16 trials reported on adverse events. none having reported a serious adverse event. Meta-analysis

demonstrated no significant differences in the incidence of any adverse events between treatment and control (RD 0.00; 95% CI -0.01 to 0.02). The quality of evidence for each outcome was determined after considering each of these elements. For the main efficacy outcome, incidence of diarrhea, the quality of evidence was categorized as low (further research is likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate) because of a high risk of bias in 2 of 7 studies in the pooled analysis (due to high loss to follow-up), and imprecision (sparse data, 225 events). For the incidence of adverse events the quality of evidence was categorized as low (our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect). However, probiotics were generally well tolerated and no serious adverse events were reported and we feel confident that the absolute effect, if it exists, is small.

Concerning the secondary outcome mean duration of diarrhea (five trials, n = 897), using an available case analysis, probiotics decreased the mean duration of diarrhea by almost three quarters of a day (WMD -0.60; 95% CI -1.18 to -0.02), a statistically significant difference. With respect to differences in mean stool frequency (four trials, n = 425), the available case results were not statistically significant (WMD -0.30 95% CI -0.60, 0.00). For the two secondary outcomes, mean duration of diarrhea and mean stool frequency, the quality of evidence was categorized as low owing to inconsistency (i.e. large statistical heterogeneity with I² of > 77%, low P value [P < 0.06], point estimates and confidence intervals vary considerably) and imprecision (e.g. confidence intervals include effect estimates that are of questionable patient importance). Furthermore, results for mean duration of diarrhea may be misleading given our suspicion of selective reporting bias. In particular, the majority of studies fail to report results for this key outcome that otherwise would be expected to have been evaluated. A previous review of RCTs of acute diarrhea reported that duration of diarrhea was the most common primary outcome (72/138 trials, 52% of trials) and this was reported in almost all trials as either a primary or secondary outcome ([Johnston 2010](#)). In this review, only 5 of 16 trials reported duration of diarrhea as a primary or secondary outcome.

This systematic review has several strengths. We asked a clear clinical question and the search strategy for this review was comprehensive including any relevant trials irrespective of language or publication status (i.e. we included unpublished data from [Destura unpublished](#) and obtained pediatric specific data from [Conway 2007](#)). Additional strengths of the review include its rigorous application of the GRADE criteria for each of the outcomes ([Guyatt 2008](#)) and the rigorous evaluation of each of the five subgroups (i.e. probiotic species, probiotic dose, antibiotic class, risk of bias and definition of diarrhea) using the 11 criteria for assessing subgroup credibility ([Sun 2010](#)).

This review also has limitations. The United European Gastroenterology Week, North American Society for Pediatric Gastroenterology, and Hepatology and Nutrition conference proceedings were not searched. In addition, although we previously did a more comprehensive search of the grey literature, for our update search we did not search conference proceedings or dissertation abstracts. Some readers may question the pooling of different probiotic species. In keeping with the justification for the combining of probiotic species used in two trials included in this review ([Tankanow 1990](#) administered both *L. acidophilus* with *L. bulgaricus*; [Jirapinyo 2002](#) administered both *L. acidophilus* with *B. infantis*; [Szymanski 2008](#) administered a cocktail of *B. longum*, *L. rhamnosus* and *L. plantarum*), data were pooled because the probiotics used in each trial share the recommended characteristics of a viable probiotic: non-pathogenic properties (noting that further study is needed on *L. sporogenes*), the ability to survive transit through the gastrointestinal tract, adherence to intestinal epithelium, colonization in the intestinal tract, production of antimicrobial substances, and a good shelf life in food or powdered form ([Goldin 1998](#)).

AUTHORS' CONCLUSIONS

Implications for practice

Despite heterogeneity in probiotic strain, dose, and duration, and study quality issues (risk of bias), the overall evidence suggests a protective effect of probiotics in preventing AAD. A test for heterogeneity indicates that a dose-response gradient explains some of the statistical heterogeneity. Using 11 criteria to evaluate the credibility of the subgroup analysis on probiotic dose, available case results indicate that the subgroup effect based on dose (≥ 5 billion CFU/day) was credible, demonstrating a large, precise benefit of high dose probiotics (RR 0.40; 95% CI 0.29 to 0.55). Based on high-dose probiotics, the number needed to treat (NNT) to prevent one case of diarrhea is seven (NNT 7; 95% CI 6 to 10). However, the extreme plausible ITT analysis was marginally significant for high dose probiotics (RR 0.72; 95% CI 0.53 to 0.99). The use of *Lactobacillus rhamnosus* or *Saccharomyces boulardii* at 5 to 40 billion colony forming units/day may be appropriate given the modest NNT and the likelihood that adverse events are very rare. It is premature to draw conclusions about the efficacy and safety of other probiotic agents for pediatric AAD. Although no serious adverse events were observed amongst the otherwise healthy children included in this pool of trials, moderate to serious adverse events have been observed in severely debilitated or immuno-compromised children with underlying risk factors including central venous catheter use and disorders associated with bacterial/fungal translocation. Until further research has been conducted, probiotic use should be avoided in pediatric populations at risk for adverse events.

Implications for research

The GRADE analysis indicated that the overall quality of the evidence for the primary endpoint for high dose probiotic studies (incidence of diarrhea) was low due to a high risk of bias in the pooled analysis (high loss to follow-up: 29% in two studies and 16% across the seven studies) and imprecision (sparse data, 225 events). The benefit for high dose probiotics (*Lactobacillus rhamnosus* or *Saccharomyces boulardii*) needs to be confirmed by a large well designed RCT. More refined trials are also needed that test strain specific probiotics and evaluate the efficacy (e.g. incidence and duration of diarrhea) and safety of probiotics with limited losses to follow-up. In particular, trials should look to determine the effect of strain

specific probiotics on: 1. incidence of diarrhea and duration of diarrhea using appropriate definitions of diarrhea onset (incidence of diarrhea) and offset (duration of diarrhea), 2. define potential adverse events a priori and monitor for these adverse reactions according to available guidelines ([Ioannidis 2004](#)) and 3. given the relatively short follow-up time in trials of this nature - limit losses to follow-up. In addition, future trials would benefit from a standard, core set of outcomes in acute diarrhea trials that are valid and reliable ([Clarke 2007](#); [Johnston 2010](#)). This would make trials more comparable and help avoid selective reporting bias.

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NOTES

REFERENCES

References to studies included in this review

Arvola 1999 *{published data only}*

Arvola T, Laiho K, Torkkeli S, Mykkanen H, Salminen S, Maunula L. Prophylactic Lactobacillus GG reduces antibiotic-associated diarrhea in children with respiratory infections: a randomized study. *Pediatrics* 1999;104:e64-.

Benhamou 1999 *{published data only}*

Benhamou PH, Berlier P, Danjou G, Plique O, Jessueld D, DuPont C. Antibiotic-associated diarrhoea in children: A computer monitored double-blind outpatients trial comparing a protective and a probiotic agent. *Médecine & Chirurgie Digestives* 1999;28:163-8.

Contardi 1991 *{published data only}*

Contardi I. Oral bacterial therapy in prevention of antibiotic-induced diarrhea in childhood. *Clinica Terapeutica* 1991;136:409-13.

Conway 2007 *{published data only}*

Conway S, Hart A, Clark A, Harvey I. Does eating yogurt prevent antibiotic-associated diarrhoea? A placebo-controlled randomised controlled trial in general practice. *British Journal of General Practice* 2007;57:953-9.

Correa 2005 *{published data only}*

Corrêa NB, Péret Filho LA, Penna FJ, Lima FM, Nicoli JR. A randomized formula controlled trial of Bifidobacterium lactis and Streptococcus thermophilus for prevention of antibiotic-associated diarrhea in infants. *Journal of Clinical Gastroenterology* 2005;39:385-9.

Destura unpublished *{published data only}*

Destura RV. Bacillus clausii in preventing antibiotic-associated diarrhea among Filipino infants and children: A multi-center, randomized, open-label clinical trial of efficacy and safety. :-.

Erdeve 2004 *{published data only}*

Erdeve O, Tiras U, Dallar Y. The probiotic effect of Saccharomyces boulardii in a pediatric age group. *Journal of Tropical Pediatrics* 2004;50:234-6.

Jirapinyo 2002 *{published data only}*

Jirapinyo P, Densupsoontorn N, Thamonsiri N, Wongarn R. Prevention of antibiotic-associated diarrhea in infants by probiotics. *Journal of the Medical Association of Thailand* 2002;85 Suppl 2:s739-42.

Kotowska 2005 {published data only}

Kotowska M, Albrecht P, Szajewska H. *Saccharomyces boulardii* in the prevention of antibiotic-associated diarrhoea in children: a randomized double-blind placebo-controlled trial. *Alimentary Pharmacology and Therapeutics* 2005;21:583-90.

LaRosa 2003 {published data only}

LaRosa M, Bottaro G, Gulino N, Gambuzza F, Forti F, Ini G. Prevention of antibiotic-associated diarrhea with *Lactobacillus sporogens* and fructo-oligosaccharides in children: A multicentric double-blind vs placebo study. *Minerva Pediatrica* 2003;55:447-52.

Merenstein 2009 {published data only}

Merenstein DJ, Foster J, D'Amico F. A randomized clinical trial measuring the influence of kefir on antibiotic-associated diarrhea: the measuring the influence of Kefir (MILK) Study. *Archives of Pediatrics & Adolescent Medicine* 2009;163:750-4.

Ruszczyński 2008 {published data only}

Ruszczyński M, Radzikowski A, Szajewska H. Clinical trial: effectiveness of *Lactobacillus rhamnosus* (strains E/N, Oxy and Pen) in the prevention of antibiotic-associated diarrhoea in children. *Alimentary Pharmacology and Therapeutics* 2008;28:154-61.

Szajewska 2009 {published data only}

Szajewska H, Albrecht P, Topczewska-Cabanek A. Randomized, double-blind, placebo-controlled trial: effect of *Lactobacillus GG* supplementation on *Helicobacter pylori* eradication rates and side effects during treatment in children. *Journal of Pediatric Gastroenterology and Nutrition* 2009;48:431-6.

Szymański 2008 {published data only}

Szymański H, Armańska M, Kowalska-Duplaga K, Szajewska H. *Bifidobacterium longum* PL03, *Lactobacillus rhamnosus* KL53A, and *Lactobacillus plantarum* PL02 in the prevention of antibiotic-associated diarrhea in children: a randomized controlled pilot trial. *Digestion* 2008;78:13-7.

Tankanow 1990 {published data only}

Tankanow RM, Ross MB, Ertel IJ, Dickinson DG, McCormick LS, Garfinkel JF. A double-blind, placebo-controlled study of the efficacy of Lactinex in the prophylaxis of amoxicillin-induced diarrhea. *DICP: The Annals of Pharmacotherapy* 1990;24:382-4.

Vanderhoof 1999 {published data only}

Vanderhoof JA, Whitney DB, Antonson DL, Hanner TL, Lupo JV, Young RJ. *Lactobacillus GG* in the prevention of antibiotic-associated diarrhea in children. *Journal of Pediatrics* 1999;135:564-8.

* indicates the major publication for the study

References to studies excluded from this review

Beausoleil 2007 {published data only}

Beausoleil M, Fortier N, Guénette S, L'ecuyer A, Savoie M, Franco M. Effect of a fermented milk combining *Lactobacillus acidophilus* C1285 and *Lactobacillus casei* in the prevention of antibiotic-associated diarrhea: a randomized, double-blind, placebo-controlled trial. *Canadian Journal of Gastroenterology* 2007;21:732-6.

Brunser 2006 {published data only}

Brunser O, Gotteland M, Cruchet S, Figueroa G, Garrido D, Steenhout P. Effect of a milk formula with prebiotics on the intestinal microbiota of infants after an antibiotic treatment. *Pediatric Research* 2006;59:451-6.

Can 2006 {published data only}

Can M, Besirbellioglu BA, Avci IY, Beker CM, Pahsa A. Prophylactic *Saccharomyces boulardii* in the prevention of antibiotic-associated diarrhea: a prospective study. *Medical Science Monitor* 2006;12:PI19-22.

Chapoy 1985 {published data only}

Chapoy P. Treatment of acute infantile diarrhea: controlled trial of *Saccharomyces boulardii*. *Annales de Pédiatrie* 1985;32:561-3.

Czerwionka 2006 {published data only}

Czerwionka-Szaflarska M, Kuczynska R, Mierzwa G, Bala G, Murawska S. Effect of probiotic bacteria supplementation on the tolerance of helicobacter pylori eradication therapy in children and youth. *Pediatrica Polska* 2006;81:334-41.

Erdeve 2005 {published data only}

Erdeve O, Tiras U, Dallar Y, Savas S. *Saccaromyces boulardii* and antibiotic-associated diarrhoea in children. *Alimentary Pharmacology and Therapeutics* 2005;21:1508-9.

Honeycutt 2007 {published data only}

Honeycutt TC, Khashab M, Wardrop RM, McNeal-Trice K, Honeycutt AL, Christy CG. Probiotic administration and the incidence of nosocomial infection in pediatric intensive care: a randomized placebo-controlled trial. *Pediatric Critical Care Medicine* 2007;8:452-8.

Kim 2008 {published data only}

Kim MN, Kim N, Lee SH, Park YS, Hwang JH, Kim JW. The effects of probiotics on PPI-triple therapy for *Helicobacter pylori* eradication. *Helicobacter* 2008;13:261-8.

Koning 2008 {published data only}

Koning CJ, Jonkers DM, Stobberingh EE, Mulder L, Rombouts FM, Stockbrügger RW. The effect of a multispecies probiotic on the intestinal microbiota and bowel movements in healthy volunteers taking the antibiotic amoxycillin. *American Journal of Gastroenterology* 2008;103:178-89.

Lei 2006 {published data only}

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

Lionetti 2006 {published data only}

Lionetti E, Miniello VL, Castellaneta SP, Magistá AM, Canio A, Maurogiovanni G. *Lactobacillus reuteri* therapy to reduce side-effects during anti-*Helicobacter pylori* treatment in children: a randomized placebo controlled trial. *Alimentary Pharmacology and Therapeutics* 2006;24:1461-8.

McFarland 2005 {published data only}

McFarland LV. Can *Saccharomyces boulardii* prevent antibiotic-associated diarrhea in children?. *Nature Clinical Practice Gastroenterology & Hepatology* 2005;2:262-3.

Michielutti 1996 {published data only}

Michielutti F, Bertini B, Presciuttini B, Andreotti G. Clinical assessment of a new oral bacterial treatment for children with acute diarrhea. *Minerva Medica* 1996;87:545-50.

Savas-Erdeve 2009 {published data only}

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

Schrezenmeir 2004 {published data only}

Schrezenmeir J, Heller K, McCue M, Llamas C, Lam W, Burow H. Benefits of oral supplementation with and without synbiotics in young children with acute bacterial infections. *Clinical Pediatrics* 2004;43:239-49.

Seki 2003 {published data only}

Seki H, Shiohara M, Matsumura T, Miyagawa N, Tanaka M, Komiyama A. Prevention of antibiotic-associated diarrhea in children by *Clostridium butyricum* MIYAIRI. *Pediatrics International* 2003;45:86-90.

Siitonen 1990 {published data only}

Siitonen S, Vapaatalo H, Salminen S, Gordin A, Saxelin M, Wikberg R. Effect of *Lactobacillus GG* yoghurt in prevention of antibiotic associated diarrhoea. *Annals of Medicine* 1990;22:57-9.

Srinivasan 2006 {published data only}

Srinivasan R, Meyer R, Padmanabhan R, Britto J. Clinical safety of *Lactobacillus casei shirota* as a probiotic in critically ill children. *Journal of Pediatric Gastroenterology and Nutrition* 2006;42:171-3

efficacy in children. *Journal of Pediatric Gastroenterology and Nutrition* 2005;42:174-8.

Sykora 2005 {published data only}

Sykora J, Valeckova K, Amlerova J, Siala K, Dedek P, Watkins S. Effects of a specially designed fermented milk product containing probiotic *Lactobacillus casei* DN-114 001 and the eradication of *H. pylori* in children: a prospective randomized double-blind study. *Journal of Clinical Gastroenterology* 2005;39:692-8.

Thomas 2001 {published data only}

Thomas MR, Litin SC, Osmon DR, Corr AP, Weaver AL, Lohse CM. Lack of effect of *Lactobacillus GG* on antibiotic-associated diarrhea: a randomized, placebo-controlled trial. *Mayo Clinic Proceedings* 2001;76:883-9.

Weizman 2005 {published data only}

Weizman Z, Asli G, Alsheikh A. Effect of a probiotic infant formula on infections in child care centers: comparison of two probiotic agents. *Pediatrics* 2005;115:5-9.

Wenus 2008 {published data only}

Wenus C, Goll R, Loken EB, Biong AS, Halvorsen DS, Florholmen J. Prevention of antibiotic-associated diarrhoea by a fermented probiotic milk drink. *European Journal of Clinical Nutrition* 2008;62:299-301.

Witsell 1995 {published data only}

Witsell DL, Garrett CG, Yarbrough WG, Dorrestein SP, Drake AF, Weissler MC. Effect of *Lactobacillus acidophilus* on antibiotic-associated gastrointestinal morbidity: a prospective randomized trial. *Journal of Otolaryngology* 1995;24:230-3.

Zoppi 2001 {published data only}

Zoppi G, Cinquetti M, Benini A, Bonamini E, Minelli EB. Modulation of the intestinal ecosystem by probiotics and lactulose in children during treatment with ceftriaxone. *Current Therapeutic Research* 2001;62:418-35.

Additional references

Akl 2009

Akl EA, Briel M, You JJ, Lamontagne F, Gangji A, Cukierman-Yaffe T. LOST to follow-up Information in Trials (LOST-IT): a protocol on the potential impact. *Trials* 2009;10:40-.

Bartlett 1978

Bartlett JG, Chang TW, Gurwith M, Gorbach SL, Onderdonk AB. Antibiotic-associated pseudomembranous colitis due to toxin-producing clostridia. *New England Journal of Medicine* 1978;298:531-4.

Beausoleil 2007

Beausoleil M, Fortier N, Guénette S, L'ecuyer A, Savoie M, Franco M. Effect of a fermented milk combining *Lactobacillus acidophilus* CL1285 and *Lactobacillus casei* in the prevention of antibiotic-associated diarrhea: A randomized, double-blind, placebo-controlled trial. *Canadian Journal of Gastroenterology* 2007;21:732-6.

Begg 1994

Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994;50:1088-101.

Berrington 2004

Berrington A, Borriello SP, Brazier J, Duckworth G, Foster K, Freeman R. National *Clostridium difficile* Standards Group: Report to the Department of Health. *Journal of Hospital Infection* 2004;56 Suppl 1:1-38.

Bin-Nun 2005

Bin-Nun A, Bromiker R, Wilschanski M, Kaplan M, Rudensky B, Caplan M. Oral probiotics prevent necrotizing enterocolitis in very low birth weight neonates. *Journal of Pediatrics* 2005;147:192-6.

Borriello 2003

Borriello SP, Hammes WP, Holzapfel W, Marteau P, Schrezenmeir J, Vaara M. Safety of probiotics that contain lactobacilli or bifidobacteria. *Clinical Infectious Diseases* 2003;36:775-80.

Clarke 2007

Clarke M. Standardising outcomes for clinical trials and systematic reviews. *Trials* 2007;8:39-.

Cremonini 2002

Cremonini F, Caro S, Nista EC, Bartolozzi F, Capelli G, Gasbarrini G. Meta-analysis: the effect of probiotic administration on antibiotic-associated diarrhoea. *Alimentary Pharmacology and Therapeutics* 2002;16:1461-7.

Cunningham-Rundles 2000

Cunningham-Rundles S, Ahrne S, Bengmark S, Johann-Liang R, Marshall F, Metakis L. Probiotics and immune response. *American Journal of Gastroenterology* 2000;95:S22-5.

D'Souza 2002

D'Souza AL, Rajkumar C, Cooke J, Bulpitt CJ. Probiotics in the prevention of antibiotic associated diarrhoea: meta-analysis. *BMJ* 2002;324:1361-6.

Davis 2010

Davis LM, Martinez I, Walter J, Hutkins R. A dose dependent impact of prebiotic galactooligosaccharides on the intestinal microbiota of healthy adults. *International Journal of Food Microbiology* 2010;144:285-92.

Duval 2001

Duval S, Tweedie R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics* 2001;56:455-63.

Egger 1997

Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629-34.

Elstner 1983

Elstner CL, Lindsay AN, Book LS, Matsen JM. Lack of relationship of *Clostridium difficile* to antibiotic-associated diarrhea in children. *Pediatric Infectious Disease* 1983;2:364-6.

Gibson 1998

Gibson GR. Dietary modulation of the human gut microflora using prebiotics. *British Journal of Nutrition* 1998;80:S209-12.

Gibson 2004

Gibson GR, Probert HM, Loo JV, Rastall RA, Roberfroid MB. Dietary modulation of the human colonic microbiota: Updating the concept of prebiotics. *Nutrition Research Reviews* 2004;17:259-75.

Gogate 2005

Gogate A, De A, Nanivadekar R, Mathur M, Saraswathi K, Jog A. Diagnostic role of stool culture and toxin detection in antibiotic associated diarrhoea due to *Clostridium difficile* in children. *Indian Journal of Medical Research* 2005;122:518-24.

Goldin 1998

Goldin BR. Health benefits of probiotics. *British Journal of Nutrition* 1998;80:S203-7.

Guyatt 2008

Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schünemann HJ. What is "quality of evidence" and why is it important to clinicians?. *BMJ* 2008;336:995-8.

Hammerman 2006

Hammerman C, Bin-Nun A, Kaplan M. Safety of probiotics: comparison of two popular strains. *BMJ* 2006;333:1006-8.

Hartling 2009

Hartling L, Ospina M, Liang Y, Dryden DM, Hooton N, Krebs Seida J. Risk of bias versus quality assessment of randomised controlled trials: cross sectional study. *BMJ* 2009;339:b4012-.

Hata 1988

Hata D, Yoshida A, Ohkubo H, Mochizuki Y, Hosoki Y, Tanaka R. Meninaitis caused by bifidobacterium in an

infant. *Pediatric Infectious Disease Journal* 1988;7:669-71.

Higgins 2003

Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557-60.

Hollis 1999

Hollis S, Campbell F. What is meant by intention to treat analysis? Survey of published randomised controlled trials. *BMJ* 1999;319:670-4.

Ioannidis 2004

Ioannidis JP, Evans SJ, Gøtzsche PC, O'Neill RT, Altman DG, Schulz K. Better reporting of harms in randomized trials: an extension of the CONSORT statement. *Annals of Internal Medicine* 2004;141:781-8.

Ioannidis 2007

Ioannidis JP, Trikalinos TA. The appropriateness of asymmetry tests for publication bias in meta-analyses: a large survey. *CMAJ* 2007;176:1091-6.

Ioannidis 2008

Ioannidis JP. Interpretation of tests of heterogeneity and bias in meta-analysis. *Journal of Evaluation in Clinical Practice* 2008;14:951-7.

Johnston 2006

Johnston BC, Supina AL, Vohra S. Probiotics for pediatric antibiotic-associated diarrhea: a meta-analysis of randomized placebo-controlled trials. *CMAJ* 2006;175:377-83.

Johnston 2007

Johnston BC, Supina AL, Ospina M, Vohra S. Probiotics for the prevention of pediatric antibiotic-associated diarrhea. *Cochrane Database of Systematic Reviews* 2007:-.

Johnston 2010

Johnston BC, Shamseer L, Costa BR, Tsuyuki RT, Vohra S. Measurement issues in trials of pediatric acute diarrheal diseases: a systematic review. *Pediatrics* 2010;126:e222-31.

Kale-Pradhan 2010

Kale-Pradhan PB, Jassal HK, Wilhelm SM. Role of *Lactobacillus* in the prevention of antibiotic-associated diarrhea: a meta-analysis. *Pharmacotherapy* 2010;30:119-26.

Land 2005

Land MH, Rouster-Stevens K, Woods CR, Cannon ML, Cnota J, Shetty AK. *Lactobacillus* sepsis associated with probiotic therapy. *Pediatrics* 2005;115:178-81.

Lau 2006

Lau J, Ioannidis JP, Terrin N, Schmid CH, Olkin I. The case of the misleading funnel plot. *BMJ* 2006;333:597-600.

Lin 2005

Lin HC, Su BH, Chen AC, Lin TW, Tsai CH, Yeh TF. Oral probiotics reduce the incidence and severity of necrotizing enterocolitis in very low birth weight infants. *Pediatrics* 2005;115:1-4.

Mackay 1999

Mackay AD, Taylor MB, Kibbler CC, Hamilton-Miller JM. *Lactobacillus* endocarditis caused by a probiotic organism. *Clinical Microbiology and Infection* 1999;5:290-2.

Madsen 2001

Madsen KL. The use of probiotics in gastrointestinal disease. *Canadian Journal of Gastroenterology* 2001;15:817-22.

McFarland 1998

McFarland LV. Epidemiology, risk factors and treatments for antibiotic-associated diarrhea. *Digestive Diseases* 1998;16:292-307.

PROBIOSES 1999/2012/2011

McFarland 2006

McFarland LV. Meta-analysis of probiotics for the prevention of antibiotic associated diarrhea and the treatment of *Clostridium difficile* disease. *American Journal of Gastroenterology* 2006;101:812-22.

McFarland 2008

McFarland LV. Antibiotic-associated diarrhea: epidemiology, trends and treatment. *Future Microbiology* 2008;3:563-78.

McFarland 2010

McFarland LV. Systematic review and meta-analysis of *Saccharomyces boulardii* in adult patients. *World Journal of Gastroenterology* 2010;16:2202-22.

Owens 2008

Owens RC, Donskey CJ, Gaynes RP, Loo VG, Muto CA. Antimicrobial-associated risk factors for *Clostridium difficile* infection. *Clinical Infectious Diseases* 2008;46 Suppl 1:S19-31.

Piarroux 1999

Piarroux R, Millon L, Bardouet K, Vagner O, Koenig H. Are live *saccharomyces* yeasts harmful to patients?. *Lancet* 1999;353:1851-2.

Rautio 1999

Rautio M, Jousimies-Somer H, Kauma H, Pietarinen I, Saxelin M, Tynkkynen S. Liver abscess due to a *Lactobacillus rhamnosus* strain indistinguishable from *L. rhamnosus* strain GG. *Clinical Infectious Diseases* 1999;28:1159-60.

Raza 1995

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

Roberfroid 1998

Roberfroid MB. Prebiotics and synbiotics: concepts and nutritional properties. *British Journal of Nutrition* 1998;80:S197-202.

Saavedra 1999

Saavedra JM. Probiotics plus antibiotics: regulating our bacterial environment. *Journal of Pediatrics* 1999;135:535-7.

Salminen 1998

Salminen S, Wright A, Morelli L, Marteau P, Brassart D, Vos WM. Demonstration of safety of probiotics -- a review. *International Journal of Food Microbiology* 1998;44:93-106.

Salminen 2004

Salminen MK, Rautelin H, Tynkkynen S, Poussa T, Saxelin M, Valtonen V. *Lactobacillus* bacteremia, clinical significance, and patient outcome, with special focus on probiotic *L. rhamnosus* GG. *Clinical Infectious Diseases* 2004;38:62-9.

Savas-Erdeve 2009

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

Saxelin 1996

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

Sazawal 2006

Sazawal S, Hiremath G, Dhingra U, Malik P, Deb S, Black RE. Efficacy of probiotics in prevention of acute diarrhoea: a meta-analysis of masked, randomised, placebo-controlled trials. *Lancet Infectious Diseases* 2006;6:374-82.

Schrotenboer 2001

Schrezenmeier 2001

Schrezenmeier J, Vrese M. Probiotics, prebiotics, and synbiotics -- approaching a definition. *American Journal of Clinical Nutrition* 2001;73:361S-4S.

Sun 2010

Sun X, Briel M, Walter S, Guyatt GH. Is a subgroup effect believable? Updating criteria to evaluate the credibility of subgroup analyses. *BMJ* 2010;340:c117-.

Sussman 1986

Sussman JI, Baron EJ, Goldberg SM, Kaplan MH, Pizzarello RA. Clinical manifestations and therapy of *Lactobacillus* endocarditis: report of a case and review of the literature. *Reviews of Infectious Diseases* 1986;8:771-6.

Szajewska 2005

Szajewska H, Mrukowicz J. Meta-analysis: non-pathogenic yeast *Saccharomyces boulardii* in the prevention of antibiotic-associated diarrhoea. *Alimentary Pharmacology and Therapeutics* 2005;22:365-72.

Szajewska 2006

Szajewska H, Ruszczyński M, Radzikowski A. Probiotics in the prevention of antibiotic-associated diarrhea in children: a meta-analysis of randomized controlled trials. *Journal of Pediatrics* 2006;149:367-72.

Turck 2003

Turck D, Bernet JP, Marx J, Kempf H, Giard P, Walbaum O. Incidence and risk factors for of oral antibiotic-associated diarrhea in an outpatient pediatric population. *Journal of Pediatric Gastroenterology and Nutrition* 2003;37:22-6.

Wenus 2008

Wenus C, Goll R, Loken EB, Biong AS, Halvorsen DS, Florholmen J. Prevention of antibiotic-associated diarrhoea by a fermented probiotic milk drink. *European Journal of Clinical Nutrition* 2008;62:299-301.

Whelan 2010

Whelan K, Myers CE. Safety of probiotics in patients receiving nutritional support: a systematic review of case reports, randomized controlled trials, and nonrandomized trials. *American Journal of Clinical Nutrition* 2010;91:687-703.

Wistrom 2001

Wistrom J, Norrby SR, Myhre EB, Eriksson S, Granstrom G, Lagergren L. Frequency of antibiotic-associated diarrhoea in 2462 antibiotic-treated hospitalized patients: a prospective study. *Journal of Antimicrobial Chemotherapy* 2001;47:43-50.

GRAPHS**Graphs and Tables**

To view a graph or table, click on the outcome title of the summary table below.

Incidence of Diarrhea

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of Diarrhea: Complete case	15	2874	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.38, 0.72]
1.1 Incidence of Diarrhea: Active controlled trials	2	773	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.33, 2.21]
1.2 Incidence of Diarrhea: Placebo controlled trials	10	1206	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.33, 0.67]

			95% CI)	0.001
1.3 Incidence of Diarrhea: No treatment control	3	895	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.19, 1.32]
<u>2 Incidence of Diarrhea: Probiotic dose</u>	14	2856	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.38, 0.74]
2.1 ≥5 billion CFU of probiotic/day	7	1474	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.29, 0.55]
2.2 <5 billion CFU of probiotic/day	7	1382	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.53, 1.21]
<u>3 Incidence of Diarrhea: Probiotic species</u>	15	2874	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.38, 0.72]
3.1 Lactobacillus rhamnosus (strains: GG and E/N, Oxy, Pen)	4	611	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.22, 0.56]
3.2 L. acidophilus & L. bulgaricus	1	38	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.61, 1.50]
3.3 L. acidophilus and Bifidobacterium infantis	1	18	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.18, 1.21]
3.4 L. sporogenes	1	98	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.29, 0.77]
3.5 Saccharomyces boulardii	3	1328	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.14, 1.48]
3.6 B. lactis & S. thermophilus	1	157	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.29, 0.95]
3.7 Bacillus clausii	1	323	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.11, 1.62]
3.8 Lactococcus lactis, L. plantarum, L. rhamnosus, L. casei, L. lactis subspecies diacetylactis, Leuconostoc cremoris, Bifidobacterium longum, B. breve, Lactobacillus acidophilus, and Saccharomyces florentinus	1	117	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.41, 1.67]
3.9 Bifidobacterium longum PL03, Lactobacillus rhamnosus KL53A, and Lactobacillus plantarum PL02	1	78	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.04, 5.03]
3.10 Streptococcus thermophilus, L. acidophilus, B. anamalis subsp. lactus, L. delbrueckii subsp. bulgaris	1	106	Risk Ratio (M-H, Random, 95% CI)	1.73 [0.39, 7.70]

			95% CI)	
4 Incidence of Diarrhea: Risk of Bias	15	2874	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.38, 0.72]
4.1 Low Risk	8	1188	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.34, 0.60]
4.2 High Risk	7	1686	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.37, 1.13]
5 Incidence of Diarrhea: Antibiotic class (≥ 5 billion CFU/day)	3	904	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.22, 0.53]
5.1 Beta-lactams/penicillins	3	468	Risk Ratio (M-H, Random, 95% CI)	0.27 [0.15, 0.46]
5.2 Cephalosporins	2	189	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.17, 1.45]
5.3 Macrolides (azithromycin)	2	247	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.21, 1.19]
6 Incidence of Diarrhea: Definition of diarrhea	13	2739	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.35, 0.72]
6.1 ≥ 3 loose/watery/liquid stools per day for at least 2 consecutive days	8	1333	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.31, 0.63]
6.2 ≥ 3 watery/liquid stools per 24 hours	2	1082	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.15, 2.85]
6.3 ≥ 2 liquid stools per day on at least 2 occasions during study	1	188	Risk Ratio (M-H, Random, 95% CI)	0.29 [0.13, 0.63]
6.4 ≥ 2 liquid stools per 24 hr	1	98	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.29, 0.77]
6.5 ≥ 1 abnormally loose bowel movement per 24 hrs	1	38	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.61, 1.50]
7 Incidence of Diarrhea: Sensitivity analysis (complete case - fixed effects)	15	2874	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.42, 0.62]
7.1 Active controlled	2	773	Risk Ratio (M-H, Fixed,	0.87 [0.58, 1.32]

7.2 Placebo controlled	10	1206	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.36, 0.59]
7.3 No treatment control	3	895	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.24, 0.64]
8 Incidence of Diarrhea: Sensitivity analysis (extreme-plausible analysis)	15	3392	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.63, 1.04]
8.1 Active controlled	2	948	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.40, 2.86]
8.2 Placebo controlled	10	1362	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.54, 0.95]
8.3 No treatment control	3	1082	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.69, 1.38]
9 Incidence of Diarrhea: Probiotic dose (extreme-plausible analysis)	14	3374	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.64, 1.07]
9.1 ≥ 5 billion CFU of probiotic/day	7	1776	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.53, 0.99]
9.2 < 5 billion CFU of probiotic/day	7	1598	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.68, 1.51]

Adverse Events

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
1 Adverse Events: Complete case	11	1578	Risk Difference (M-H, Random, 95% CI)	0.00 [-0.01, 0.02]
2 Adverse Events: Same event rate assumptions analysis	16	3432	Risk Difference (M-H, Random, 95% CI)	0.01 [-0.00, 0.02]

Mean Stool Frequency

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
1 High Dose vs Low Dose: Complete case	4	425	Mean Difference (IV, Random, 95% CI)	-0.30 [-0.60, -9.13]
1.1 ≥ 5 billion CFU/day	2	307	Mean Difference (IV, Random, 95% CI)	-0.08 [-0.29, 0.14]
1.2 < 5 billion CFU/day	2	118	Mean Difference (IV, Random, 95% CI)	-0.50 [-0.89, -0.10]

Mean Duration of Diarrhea

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
1 High Dose vs Low Dose: Complete case	5	897	Mean Difference (IV, Random, 95% CI)	-0.60 [-1.18, -0.02]
1.1 ≥ 5 billion CFU/day	3	417	Mean Difference (IV, Random, 95% CI)	-0.70 [-1.44, 0.04]
1.2 < 5 billion CFU/day	2	480	Mean Difference (IV, Random, 95% CI)	-0.44 [-1.63, 0.75]

COVER SHEET

Probiotics for the prevention of pediatric antibiotic-associated diarrhea

Reviewer(s)	Johnston Bradley C, Goldenberg Joshua Z, Vandvik Per O, Sun Xin, Guyatt Gordon H
Contribution of Reviewer(s)	
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HISTORY

History

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