Cochrane Library

Cochrane Database of Systematic Reviews

Probiotics for the prevention of pediatric antibiotic-associated diarrhea (Review)

Goldenberg JZ, Lytvyn L, Steurich J, Parkin P, Mahant S, Johnston BC

Goldenberg JZ, Lytvyn L, Steurich J, Parkin P, Mahant S, Johnston BC.
Probiotics for the prevention of pediatric antibiotic-associated diarrhea.
Cochrane Database of Systematic Reviews 2015, Issue 12. Art. No.: CD004827.
DOI: 10.1002/14651858.CD004827.pub4.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Probiotics for the prevention of pediatric antibiotic-associated diarrhea

Joshua Z Goldenberg[1], Lyubov Lytvyn[2], Justin Steurich[3], Patricia Parkin[4], Sanjay Mahant[4], Bradley C Johnston[5]

[1]Bastyr University Research Institute, Seattle, WA, USA. [2]Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Canada. [3]Bastyr University, Seattle, WA, USA. [4]Child Health Evaluative Sciences, Hospital for Sick Children Research Institute, Toronto, Canada. [5]Systematic Overviews through advancing Research Technology (SORT), Child Health Evaluative Sciences, The Hospital for Sick Children, University of Toronto, Toronto, Canada

Contact address: Bradley C Johnston, Systematic Overviews through advancing Research Technology (SORT), Child Health Evaluative Sciences, The Hospital for Sick Children, University of Toronto, 686 Bay Street, Room 11.9859 West, Toronto, ON, M5G 0A4, Canada. bradley.johnston@sickkids.ca.

Editorial group: Cochrane IBD Group.
Publication status and date: Edited (no change to conclusions), published in Issue 12, 2015.
Review content assessed as up-to-date: 24 November 2014.

Citation: Goldenberg JZ, Lytvyn L, Steurich J, Parkin P, Mahant S, Johnston BC. Probiotics for the prevention of pediatric antibiotic-associated diarrhea. *Cochrane Database of Systematic Reviews* 2015, Issue 12. Art. No.: CD004827. DOI: 10.1002/14651858.CD004827.pub4.

ABSTRACT

Background

Antibiotics are frequently prescribed in children. They alter the microbial balance within the gastrointestinal tract, commonly resulting in antibiotic-associated diarrhea (AAD). Probiotics may prevent AAD via restoration of the gut microflora.

Objectives

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.

Search methods

MEDLINE, EMBASE, CENTRAL, CINAHL, AMED, and the Web of Science (inception to November 2014) 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, nutraceutical and 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 risk ratio (RR) or risk difference (RD), and continuous data (mean duration of diarrhea, mean daily stool frequency) as mean difference (MD), along with their corresponding 95% confidence interval (95% CI). 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, as well as risk of bias. We also conducted *post hoc* subgroup analyses by patient diagnosis, single versus multi-strain, industry sponsorship, and inpatient status. The overall quality of the evidence supporting the outcomes was evaluated using the GRADE criteria.

Main results

Twenty-three studies (3938 participants) met the inclusion criteria. Trials included treatment with either *Bacillus spp., Bifidobacterium spp., Clostridium butyricum*, *Lactobacilli spp.*, *Lactococcus spp., Leuconostoc cremoris*, *Saccharomyces spp.,* or*Streptococcus spp.,* alone or in combination. Eleven studies used a single strain probiotic, four combined two probiotic strains, three combined three probiotic strains, one combined four probiotic strains, two combined seven probiotic strains, one included ten probiotic strains, and one study included two probiotic arms that used three and two strains respectively. The risk of bias was determined to be high or unclear in 13 studies and low in 10 studies. Available case (patients who did not complete the studies were not included in the analysis) results from 22/23 trials reporting on the incidence of diarrhea show a precise benefit from probiotics compared to active, placebo or no treatment control. The incidence of AAD in the probiotic group was 8% (163/1992) compared to 19% (364/1906) in the control group (RR 0.46, 95% CI 0.35 to 0.61; I^2 = 55%, 3898 participants). A GRADE analysis indicated that the overall quality of the evidence for this outcome was moderate. This benefit remained 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) sensitivity analysis, where the incidence of AAD in the probiotic group was 14% (330/2294) compared to 19% (426/2235) in the control group (RR 0.69; 95% CI 0.54 to 0.89; I^2 = 63%, 4529 participants). None of the 16 trials (n = 2455) that reported on adverse events documented any serious adverse events attributable to probiotics. 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 0.01). The majority of adverse events were in placebo, standard care or no treatment group. Adverse events reported in the studies include rash, nausea, gas, flatulence, abdominal bloating, abdominal pain, vomiting, increased phlegm, chest pain, constipation, taste disturbance, and low appetite.

Authors' conclusions

Moderate quality evidence suggests a protective effect of probiotics in preventing AAD. Our pooled estimate suggests a precise (RR 0.46; 95% CI 0.35 to 0.61) probiotic effect with a NNT of 10. Among the various probiotics evaluated, *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 among otherwise healthy children, 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. Future trials would benefit from a standard and valid outcomes to measure AAD.

PLAIN LANGUAGE SUMMARY

Probiotics for the prevention antibiotic-associated diarrhea in children

What is antibiotic-associated diarrhea?

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.

What are probiotics?

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.

What did the researchers investigate?

The researchers investigated whether probiotics prevent AAD in children receiving antibiotic therapy and whether probiotics causes any harms (side effects). The researchers searched the medical literature extensively up to November 24, 2014.

What did the researchers find?

Twenty-three studies were reviewed and provide the best available evidence. The studies tested 3938 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 1 to 12 weeks. Analyses showed that probiotics may be effective for preventing AAD. The incidence of AAD in the probiotic group was 8% (163/1992) compared to 19% (364/1906) in the control group. Probiotics were generally well tolerated, and minor side effects occurred infrequently, with no significant difference between probiotic and control groups. The majority of side effects were reported in the placebo, standard care or no treatment groups. Side effects reported in the studies include rash, nausea, gas, flatulence, abdominal bloating, abdominal pain, vomiting, increased phlegm, chest pain, constipation, taste disturbance, and low appetite. Among the various probiotics evaluated, *Lactobacillus rhamnosus* or *Saccharomyces boulardii* at 5 to 40 billion colony forming units/day may be appropriate for preventing AAD in children receiving antibiotics. It is premature to draw conclusions about the effectiveness and safety of other probiotic agents for preventing AAD. Although no serious probiotic-related side effects were observed among the otherwise healthy children who participated in the studies, serious side effects have been observed in severely debilitated or immuno-compromised children with underlying risk factors including central venous catheter (a flexible tube used to give medicines) use and disorders associated with bacterial or fungal translocation (the passage of bacteria from the gut to other areas of the body). Until further research has been conducted, probiotic use should be avoided in children at risk for side effects.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [*Explanation*]

Probiotics as an adjunct to antibiotics for the prevention of antibiotic-associated diarrhea in children

Patient or population: Children given antibiotics
Setting: Inpatient and outpatient
Intervention: Probiotics
Comparison: Control (placebo or no active treatment)

Outcomes	Anticipated absolute effects* (95% CI)		Effect size (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with control	Risk with Probiotics				
Incidence of diarrhea Follow up: range 1 week to 12 weeks	191 per 1000	88 per 1000 (67 to 116)	RR 0.46 (0.35 to 0.61)	3898 (22 RCTs)	⊕⊕⊕◯ MODERATE[1,2]	
Adverse events Follow up: range 1 week to 4 weeks	35 per 1000	33 per 1000 (15 to 72)	RD 0.00 (-0.01 to 0.01)	2455 (16 RCTs)	⊕◯◯◯ VERY LOW[3,4,5]	
Duration of diarrhea Follow up: range 10 days to 12 weeks		The mean duration of diarrhea in the intervention group was 0.6 days fewer (1.18 fewer to 0.02 fewer)		897 (5 RCTs)	⊕⊕◯◯ LOW[6,7]	
Stool frequency Follow up: range 10 days to 12 weeks		The mean stool frequency in the intervention group was 0.3 lower (0.6 lower to 0)		425 (4 RCTs)	⊕⊕◯◯ LOW[,8,9]	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **RD:** Risk difference;

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: 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 quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] A test for interaction between low risk of bias trials and high or unclear risk of bias trials was not statistically significant. Additionally, the low risk of bias trials actually showed a more favorable effect of intervention than the high or unclear risk of bias trials.
[2] I^2 is 55% with a p value of 0.0009 suggesting substantial heterogeneity. While we explored the heterogeneity we were unable to explain it completely with our a priori or post hoc analyses.
[3] Because of widely varying definitions of adverse events there is considerable indirectness in terms of outcomes.
[4] Only 16 or 22 trials reported adverse events, suggesting selective outcome reporting bias.
[5] Sparse data (81 events).
[6] Inconsistency (large statistical heterogeneity with I^2 of 79%, low P value [P = 0.04], point estimates and confidence intervals vary considerably).
[7] The upper bound of 0.02 per day is not considered patient important.
[8] Inconsistency (large statistical heterogeneity with I^2 of 78%, low P value [P = 0.05], point estimates and confidence intervals vary considerably).
[9] 95% confidence interval includes no effect and lower bound of 0.60 per day is of questionable patient importance.

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 rarely 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 (McFarland 2008; LaRosa 2003; Wistrom 2001; McFarland 1998). The incidence of diarrhea in children receiving broad spectrum antibiotics has been reported in the range of 11 to 40% (Turck 2003; Elstner 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 butyicum*.

PREVIOUS REVIEWS ON PROBIOTICS AND AAD

Nine meta-analyses have addressed the use of probiotics, alone or in combination, for the prevention of AAD in adults and children. The results of diverse probiotic agents co-administered with antibiotics favoured probiotics (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 0.52, 95% CI 0.38 to 0.72; Johnston 2011). This systematic review is an update of a previously published Cochrane review (Johnston 2011).

SAFETY OF PROBIOTICS

The safety of diverse probiotic interventions does not appear to be a concern in healthy individuals (Hempel 2011; Whelan 2010; 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).

Three systematic reviews have addressed the safety of *Saccharomyces boulardii* (*S. boulardii)* and other probiotics (Hempel 2011; 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, such as enteral nutrition or parenteral nutrition, 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 or fungal translocation). Each of the children recovered after *S boulardii* or*Lactobacillus GG* was discontinued, after removal of the central venous catheter (n = 7) and after 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 increased virulence (Whelan 2010). The third systematic review, the largest and most comprehensive to date, assessed the safety of probiotics and included both randomized and non-randomized studies (387 studies including 24,615 total participants). Based on short-term probiotic use (compared to control group participants) results of 208 RCTs showed no statistically significant difference in the overall number of adverse events (RR 1.00; 95% CI: 0.93, 1.07), including serious adverse events (RR 1.06; 95% CI: 0.97, 1.16; 66 RCTs primarily based on *Lactobacillus* species) (Hempel 2011).

AIMS OF TREATMENT

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

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 interventions

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

In November 2014, 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 (2014) the trial registers of the Cochrane IBD/FBD Review Group, the Cochrane Complementary Medicine Field's Register of Controlled Trials, MEDLINE (1966 to 2014), EMBASE (1980 to 2014), CINAHL (1982 to 2014), AMED (1985 to 2014), Web of Science (1945 to 2014).

HANDSEARCHES

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

ADDITIONAL SEARCHES

We searched ongoing trials through ClinicalTrials.gov and NICE Evidence Services (Formerly NHS Evidence), 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.mp. or "streptococcus thermophilus".tw. or enterococcus faecium.mp., **3**. exp antibiosis/ or biotherapeutic agent$.tw., **4**. or/1-3, **5**. exp Anti-Bacterial Agents/ or antimicrobial$.tw. or antibiotic$.tw., **6**. ((antimicrobial or anti microbial or antimycrobial or antimycobacteri$ 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 preemie$ or premature$).tw., **22**. (schoolchild$ or "school child$").tw., **23**. (schoolage$ or school age$).tw., **24**. toddler$.tw., **25**. pubert$.tw., **26**. (pre-pubescen$ or prepubescen$ or post-pubescen$ or postpubescen$).tw., **27**. (kid or kids or boy$ or girl$).tw., **28**. juvenile.tw., **29**. or/10-28, **30**. 9 and 29, **31**. random$.tw., **32**. factorial$.tw., **33**. (crossover$ or cross over$ or cross-over$).tw., **34**. placebo$.tw., **35**. single blind.mp., **36**. double blind.mp., **37**. triple blind.mp., **38**. (singl$ adj blind$).tw., **39**. (double$ adj blind$).tw., **40**. (tripl$ adj blind$).tw., **41**. assign$.tw., **42**. allocat$.tw., **43**. crossover procedure/, **44**. double blind procedure/, **45**. single blind procedure/, **46**. triple blind procedure/, **47**. randomized controlled trial/, **48**. or/1-17, **49**. (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.), **50**. 48 not 49, **51**. 30 and 50[/=MeSH term, exp=explode, tw=text word, mp=multipurpose word, $=truncation]

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. 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. Di-

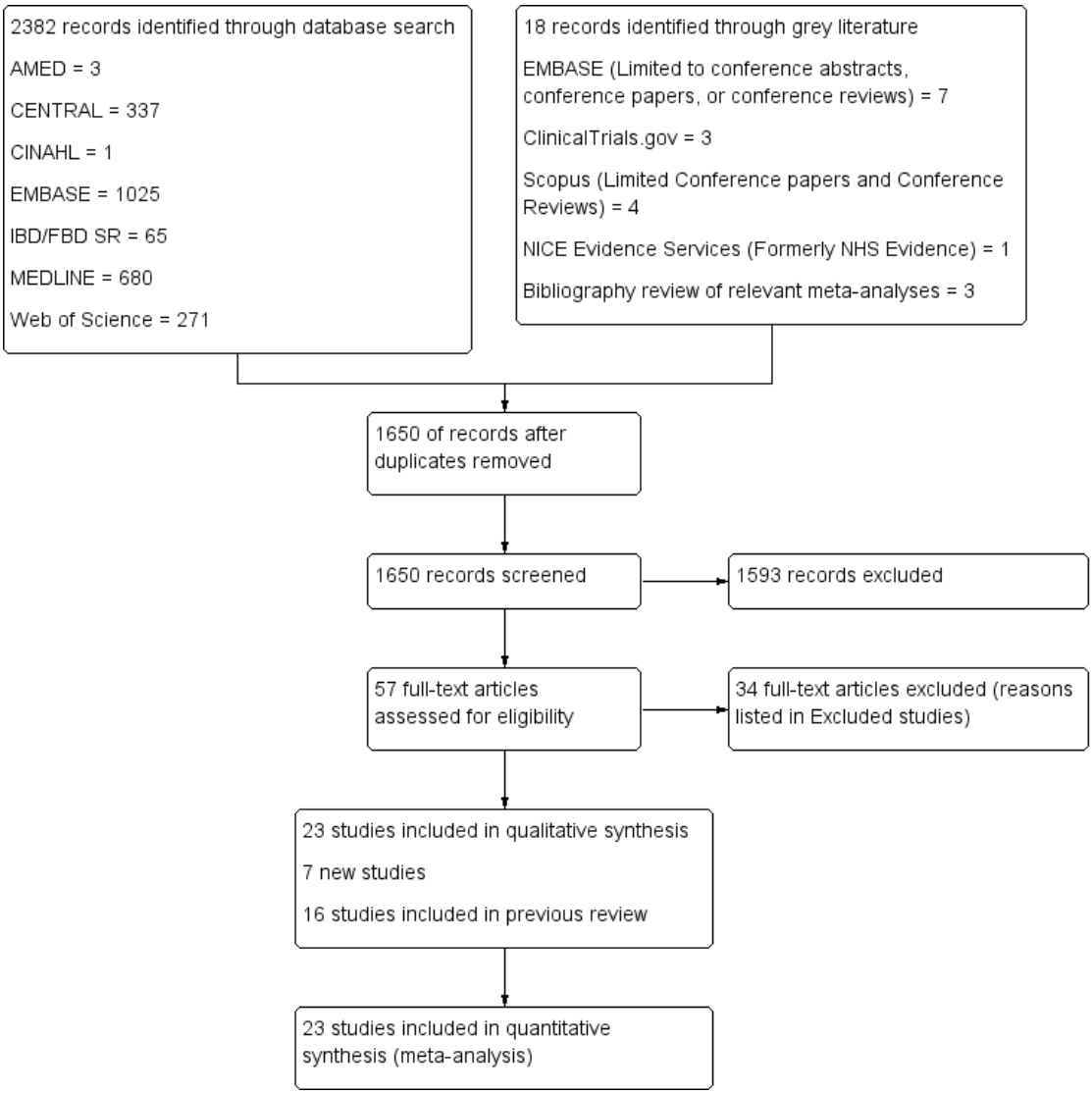
chotomous data are presented as risk ratios (RR), and continuous data as mean difference, along with corresponding 95% confidence interval (95% CI). Using control event risks from the included trials, the number needed to treat (NNT) or the number needed to harm (NNH) was calculated for statistically 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 I^2 statistic (Higgins 2003). Meta-regression or the Chi^2 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, *a priori* subgroup analyses were subdivided by: probiotic strain(s) (when two or more trials administered the same strains), diagnostic criteria for diarrhea (e.g. $\geq$ 3 watery/liquid stools per day for 2 consecutive days versus $\geq$ 3 watery/liquid stools per day), dosage of probiotic ($\geq$ 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). We also explored heterogeneity with four *post hoc* subgroups including diagnosis, industry sponsorship, inpatient versus outpatient, and single strain versus multi-strain probiotics. To assess the potential influence of missing outcome 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, a funnel plot, was 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).

RESULTS

Description of 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 November 2014. A total of 2382 studies were identified from the primary electronic databases (Medline 680, EMBASE 1025, CENTRAL 337, CINAHL 1, Web of Science 271, AMED 3, IBD/FBD SR 65). A grey literature search of EMBASE (limited to conference abstracts, conference papers, or conference reviews), ClinicalTrials.gov, Scopus (limited to conference papers and reviews), and NICE Evidence Services, as well as bibliographic review of relevant meta-analyses identified an additional 18 relevant studies. See Figure 1.

Figure 1. Study flow diagram.



Of all of these studies, 750 were identified as duplicates, leaving 1650 abstracts and titles identified as original publications. Independent review of these titles and abstracts identified 57 potentially relevant studies for full-text review. Three authors independently assessed these studies and identified 23 that met the inclusion criteria, seven of which were new since the previous version of this review (Johnston 2011). Reasons for exclusion are listed in the Characteristics of excluded studies tables.

Design

All included studies were prospective, randomized, controlled trials with placebo, active or no treatment control arms.

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 23 studies included a total of 3938 patients (2012 treatment, 1926 controls). Patients in the trials were treated with antibiotics for upper and lower respiratory tract, or ear infections (Zheng 2012; Merenstein 2009; Kotowska 2005; LaRosa 2003; Arvola 1999), *H. pylori* infection (Kodadad 2013; Saneeyan 2011; Szajewska 2009; Sykora 2005), mixed infections (Contardi 1991; Destura unpublished; Fox 2015;

Georgieva unpublished; Ruszczynski 2008; Shan 2013; Szymanski 2008; Tankanow 1990; Vanderhoof 1999)), and meningitis or septicemia (Jirapinyo 2002). In four studies the type of infection that necessitated antibiotic therapy was not specified (Benhamou 1999; Conway 2007; Correa 2005; Erdeve 2004). The health care setting was reported in 20 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; Georgieva unpublished; Shan 2013; Zheng 2012), an outpatient university teaching hospital (Kotowska 2005; Arvola 1999; Saneeyan 2011), and both inpatient and outpatient hospital populations (Destura unpublished). Two studies recruited from a hospital but it was unclear if the participants were inpatient or outpatient (Kodadad 2013; Sykora 2005). 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, and included 15 countries: Poland (Kotowska 2005; Szajewska 2009; Ruszczynski 2008; Szymanski 2008), the United States of America (Merenstein 2009; Tankanow 1990; Vanderhoof 1999), China (Shan 2013; Zheng 2012), Iran (Kodadad 2013; Saneeyan 2011), Italy (LaRosa 2003; Contardi 1991), Finland (Arvola 1999), France (Benhamou 1999), England (Conway 2007), Australia (Fox 2015), Brazil (Correa 2005), the Philippines (Destura unpublished), Turkey (Erdeve 2004), Bulgaria (Georgieva unpublished), Thailand (Jirapinyo 2002), and the Czech Republic (Sykora 2005). Children ranged from 1 month to 18 years of age. Eighteen 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), treatment 6.8 years and control 6.3 years (Fox 2015), 8.9 years (Georgieva unpublished), 9.1 years (Kodadad 2013), 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), treatment 8.2 years and control 9.5 years (Saneeyan 2011), 2 years (Shan 2013), treatment 12.6 years and control 12.9 years (Sykora 2005), 12.3 years treatment and 11.9 years control (Szajewska 2009), 2.5 years (Tankanow 1990), 4 years (Vanderhoof 1999), and 1.2 years (Zheng 2012). 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). Eighteen studies included both males and females (1439 males and 1292 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 or route was used (Merenstein 2009; Conway 2007; Destura unpublished; Georgieva 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), one study provided beta-lactams (n = 64), macrolides (n = 5), and tetracyclines (n = 1) (Fox 2015), 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). Kodadad 2013 provided all participants (n = 66) with amoxicillin and furazolidone. Szajewska 2009, Saneeyan 2011 and Sykora 2005 provided all participants (n = 200) with amoxicillin and clarithromycin. 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). Shan 2013 provided cephalosporins (n = 173), beta lactams (n = 88), and macrolides (n = 46). Zheng 2012 provided beta-lactams (n = 33), cephalosporins (n = 172), and macrolides (n = 22).

Trials included treatment with either *Bacillus spp., Bifidobacterium spp., Clostridium butyricum, 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-oligosaccaride (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); *Lactobacilluss 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); *Streptococcus thermophillus, Lactobacillus acidophilus, and Bifidobacteria anamalis* subsp. *lactus* or *Streptococcus thermophillus and Lactobacillus delbrueckii subsp. bulgaris,* 1 billion CFU bacteria/day (Conway 2007); *Lactobacillus GG*, 5.2 billion CFU/day; *Bifidobacterium bifidus*, 5.9 billion CFU/day, *Lactobacillus acidophilus* 8.3 billion CFU/day (Fox 2015); *Lactobacillus reuteri* 100 million CFU/day (Georgieva unpublished); *Lactobacillus acidophilus*, *Lactobacillus rhamnosus*, *Lactobacillus bulgaricus*, *Lactobacillus casei*, *Streptococcus thermophilus*, *Bifidobacterium infantis* and *Bifidobacterium breve* for a total of 1 billion CFU/day (Kodadad 2013); *Lactobasillus casei*, *Lactobacillus acidophilus*, *Lactobasillus reuteri*, *Lactobasillus bulgaricus*, *Streptococcus*, *Bifidobacterium bifidum*, *Bifidobacterium infantis*for a total of 1 billion CFU/day (Saneeyan 2011); *Saccharomyces boulardii,* 10 billion CFU/day (Shan 2013); *Lactobacillus casei* 10 billion CFU/day (Sykora 2005); and finally *Clostridium Butyricum* and*Bifidobacterium* at 2.2 billion CFU/day (Zheng 2012).

Comparison

In 15 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), four trials compared probiotics to no treatment (Erdeve 2004; Destura unpublished; Shan 2013; Zheng 2012), 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

Twenty-two studies (n = 3898) provided data on the incidence of diarrhea, 16 studies (n = 2455) 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 two consecutive days 48 hours after initiation of antibiotic therapy (Destura unpublished); to greater than or equal to three loose or watery stools per day for a minimum of 48 hrs, occurring during or up to two weeks after the end of the antibiotic therapy (Szajewska 2009; Ruszczynski 2008; Szymanski 2008; Georgieva unpublished; Saneeyan 2011; Shan 2013). One trial used various definitions of diarrhea which included (A) stool consistency $\geq$ 5 (as measured by the Bristol Stool Scale) and stool frequency $\geq$2/day for more than 2 days; (B) stool consistency $\geq$5 and stool frequency $\geq$3/day for more than 2 days; (C) stool consistency $\geq$ 6 and stool frequency $\geq$ 2/day for more than two days; and (D) stool consistency $\geq$ 6 and stool frequency $\geq$ 3/day for more than two days (Fox 2015). One study defined diarrhea as two or more bowel movements over the patient's baseline number of bowel movements (Zheng 2012).

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, ß-glucosidase and ß-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, or discontinuation of antibiotic treatment (Ruszczynski 2008; Szymanski 2008). Additionally, four studies reported on *H. pylori* outcomes such as positive rapid urea test, positive histopathology for *H. pylori*, and positive C13 urea breath test (Szajewska 2009; Kodadad 2013; Saneeyan 2011; Sykora 2005). 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

Loss to follow-up was substantial (i.e. > 20%) in 5/22 trials reporting on 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. Seven trials provided a flow diagram to track participants some of which included details regarding drop-outs (Kodadad 2013; Merenstein 2009; Szajewska 2009; Ruszczynski 2008; Szymanski 2008; Conway 2007; Kotowska 2005). All studies were randomized parallel group designs. Eighteen 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. Four trials were open label (Contardi 1991; Destura unpublished; Shan 2013; Zheng 2012). The validated risk of bias instrument categorizes risk into three categories: high risk of bias, low risk of bias and unclear. Ten trials were categorized as low risk (Merenstein 2009; Szajewska 2009; Ruszczynski 2008; Szymanski 2008; Correa 2005; Kotowska 2005; LaRosa 2003; Vanderhoof 1999; Fox 2015; Sykora 2005) and thirteen trials were categorized as high risk (Erdeve 2004; Jirapinyo 2002; Arvola 1999; Benhamou 1999; Contardi 1991; Tankanow 1990; Destura unpublished; Conway 2007; Georgieva unpublished, Kodadad 2013, Saneeyan 2011, Shan 2013, Zheng 2012). See Figure 2 and Figure 3 for the overall results of the risk of bias assessment.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

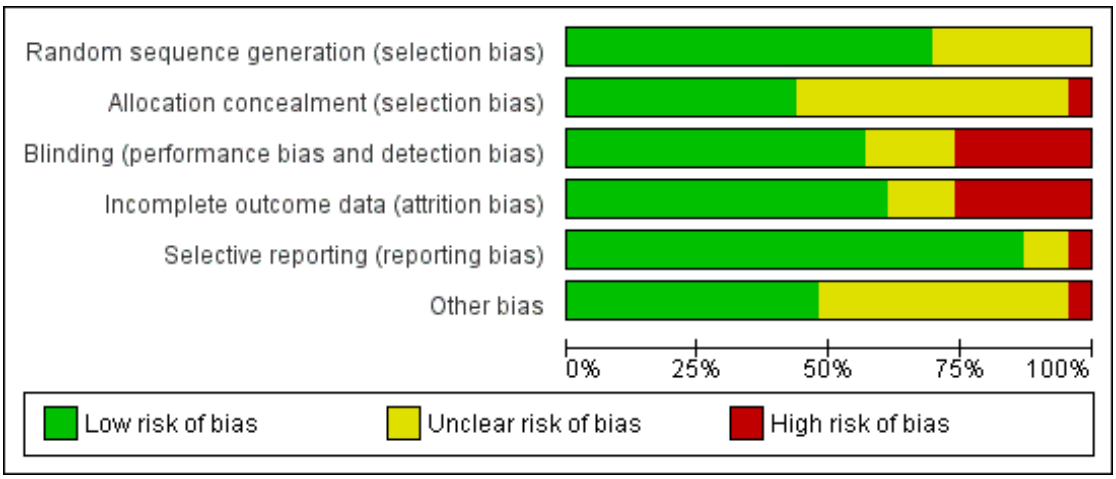
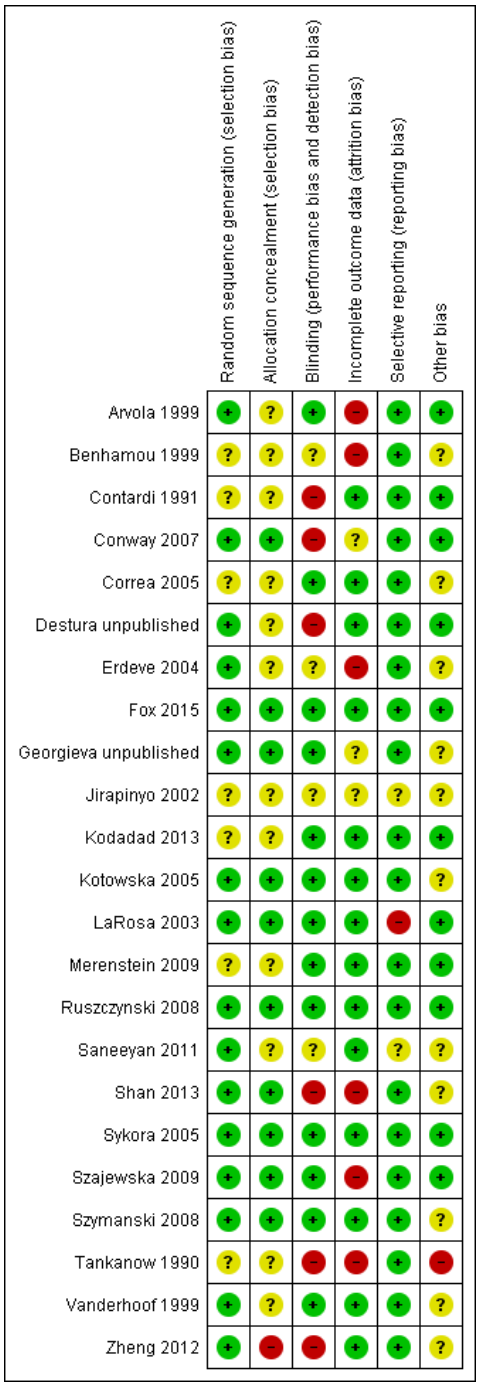


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Effects of interventions

See: **Summary of findings for the main comparison** Probiotics as an adjunct to antibiotics for the prevention of 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 or absence of diarrhea. Twenty-two studies (n = 3898) reported the 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, six placebo-controlled studies showed a statistically significant reduction in the incidence of AAD (P < 0.05) (Ruszczynski 2008; Kotowska 2005; LaRosa 2003; Vanderhoof 1999; Saneeyan 2011, Fox 2015); one active-controlled study (formula) was statistically significant (Correa 2005), and three 'no treatment-control' study demonstrated statistical significance (Erdeve 2004, Zheng 2012, Shan 2013). Nine placebo-controlled studies (Merenstein 2009; Szajewska 2009; Szymanski 2008; Jirapinyo 2002; Arvola 1999; Tankanow 1990, Georgieva unpublished, Kodadad 2013, Sykora 2005), two no treatment-control studies (Conway 2007; Destura unpublished), and one active-control (diosmectite) study (Benhamou 1999) did not show a statistically significant difference. 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 8% compared to 19% in the active, placebo or no treatment control group (3898 participants; RR 0.46; 95% CI 0.35 to 0.61; random-effects). However, statistically significant heterogeneity was detected (P = 0.0009) and this was moderate with respect to percent variability due to between (or inter -) study variability (I^2 = 55%) (Higgins 2003). A GRADE analysis indicated that the overall quality of evidence for the outcome incidence of diarrhea was moderate due to heterogeneity (see Summary of findings for the main comparison).

Adverse events

None of the studies specifically defined adverse events *a priori*. Nine reported no adverse events (Kotowska 2005; Jirapinyo 2002; Vanderhoof 1999; Shan 2013; Zheng 2012; Conway 2007; Destura unpublished, Ruszczynski 2008; Szymanski 2008). Seven trials reported adverse events (Merenstein 2009; Szajewska 2009; Correa 2005; Tankanow 1990; Fox 2015; Kodadad 2013; Sykora 2005). 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. Fox 2015 reported 14 participants with adverse events including abdominal pain, loss of appetite, nausea, vomiting and headache. More adverse events were reported in the control group than the intervention group. Kodadad 2013 reported 18 participants with adverse events including nausea, vomiting, and abdominal bloating. More adverse events occurred in the control group than the treatment group. Sykora 2005 reported 28 adverse events occurring in 16 people. However eight of the reported adverse events were diarrhea which we counted as our primary outcome. This left four participants with non-diarrhea adverse events in each group. No statistically significant difference in adverse events was found between groups. Meta-analysis of 16 trials (2455 participants) that included adverse events demonstrated no statistically significant differences in the incidence of adverse events (RD 0.00; 95% CI -0.01 to 0.01). A GRADE analysis indicated that the overall quality of evidence for this outcome was very low due to sparse data (81 events), indirectness and potential selective reporting (see Summary of findings for the main comparison).

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 weighted mean differnce (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; 897 participants). Statistically significant heterogeneity was detected (P = 0.008) and this was high with respect to percent variability due to between (or inter -) study variability (I^2 = 79%) (Higgins 2003). A GRADE analysis indicated that the overall quality of evidence for this outcome was low due to serious inconsistency (see Summary of findings for the main comparison).

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; I^2 = 78%; 425 participants). A GRADE analysis indicated that the overall quality of evidence for this outcome was low due to serious inconsistency (see Summary of findings for the main comparison).

A PRIORI SUBGROUPS

Probiotic species

Four of 22 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 four studied the yeast *Saccharomyces boulardii* (Kotowska 2005; Erdeve 2004; Benhamou 1999; Shan 2013). 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, I^2 = 0%). The summary statistic for the *Saccharomyces boulardii* trials (n = 1611) was statistically significant as well (RR 0.40; 95% CI 0.17 to 0.96, I^2 = 85%). Tests for interaction revealed trending but not statistically significant species related heterogeneity (P = 0.07).

Probiotic dose

The daily dosage of probiotic(s) varied greatly (100 million to 40 billion CFU/day). Twenty-one of 22 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; Shan 2013, Fox 2015, Sykora 2005, Georgieva unpublished, Saneeyan 2011, Zheng 2012, Kodadad 2013). The *a priori* subgroup analyses on dose compared < 5 billion CFU/day versus ≥ 5 billion CFU/day. Ten 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; Shan 2013; Sykora 2005; Fox 2015) 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 24% in the active, placebo or no treatment control group (RR 0.36; 95% CI 0.26 to 0.51; I^2 = 41%). Eleven studies providing < 5 billion CFU bacteria/yeast per day: 100 million CFU/day (Georgieva unpublished), 200 million CFU/day (Szymanski 2008), 825 million CFU/day (Correa 2005), 1 billion CFU/day (Conway 2007; Szajewska 2009; Saneeyan 2011; Kodadad 2013), 2 billion CFU/day (Tankanow 1990), 2.2 billion CFU/day (Zheng 2012), 4 billion CFU/day (Destura unpublished), and 4.5 billion CFU/day (Benhamou 1999) demonstrated statistically significant results when combined as well. For the low dose studies the pooled incidence of AAD in the probiotic group was 8% compared to 13% in the active, placebo or no treatment control group (RR 0.62; 95% CI 0.41 to 0.92; I^2 = 47%). A test for interaction did not reveal any statistically significant dose-related heterogeneity (P = 0.05; I^2 = 74.4%), although it was of borderline significance. We conducted a *post hoc* meta-regression on dose which showed a statistically significant association between CFU/day and risk reduction, with higher level of CFUs/day associated with greater risk reduction. On average one billion additional CFUs/day is associated with 1.7% (95% CI 1.5% - 1.9%) increase in RRR and 0.46% (95% CI 0.41% - 0.50%) increase in ARR, both p-values < 0.001.

Quality

Of the 22 studies reporting on incidence of diarrhea, ten 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; Sykora 2005; Fox 2015) and twelve were rated as having a high risk of bias (Conway 2007; Erdeve 2004; Jirapinyo 2002; Arvola 1999; Benhamou 1999; Tankanow 1990; Destura unpublished; Georgieva unpublished; Kodadad 2013; Saneeyan 2011; Shan 2013; Zheng 2012). 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 (RR 0.42; 95% CI 0.30 to 0.60) and high risk studies (RR 0.50; 95% CI 0.33 to 0.77). A test for interaction was not statistically significant (P = 0.54). 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 eighteen studies defining diarrhea onset/diagnosis. Twelve studies (Szajewska 2009; Ruszczynski 2008; Szymanski 2008; Conway 2007; Correa 2005; Kotowska 2005; Arvola 1999; Destura unpublished; Fox 2015; Georgieva unpublished; Saneeyan 2011; Shan 2013), defined diarrhea as ≥ 3 loose, watery, or liquid stools per day for at least two consecutive days (RR 0.37; 95% CI 0.26 to 0.51). 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). Fox 2015 used five different definitions of diarrhea and reported results separately for their definitions "A" through "E." We used their "A" definition (two or more loose, watery, or liquid stools a day for more than two days) for our primary analysis but used their "B" through "E" definitions

(three or more loose, watery, or liquid stools a day for more than two days; two or more watery or liquid stools a day for more than two days; three or more watery or liquid stools a day for more than two days; any of the previous definitions) for our subgroup analysis by diarrhea definition. Fox 2015 reported results for their "A" through "E" definitions as follows RR 0.05; 95% CI 0.01 to 0.35; RR 0.03; 95% CI 0.00 to 0.51; RR 0.06; 95% CI 0.00 to 1.04; RR 0.08; 95% CI 0.00 to 1.39; RR 0.04; 95% CI 0.01 to 0.27, respectively. A test for interaction by diarrhea definition was statistically significant (P = 0.0009). When the data from the Fox 2015 trial were limited to a single definition the test for interaction was still statistically significant (P = 0.02). Using 11 criteria to evaluate the credibility of the subgroup analysis, the results indicate that the subgroup effect based on definition was plausible (Sun 2010; See Appendix 1).

POST HOC SUBGROUPS

There was moderate heterogeneity in the primary meta-analysis (I^2 = 55%). *A priori* subgroup analysis investigating this heterogeneity identified some causes, such as definition of diarrhea, but to better explain the heterogeneity we also investigated the following *post hoc* subgroups: diagnosis type, industry sponsorship, inpatient versus outpatient, and single versus multi strain interventions.

Diagnosis

Nineteen studies reported on the participants' diagnoses which had necessitated the antibiotics. Five studies were limited to upper respiratory infections (Arvola 1999; Merenstein 2009; LaRosa 2003; Kotowska 2005; Zheng 2012). Four studies were limited to participants with *H. pylori* infections (Kodadad 2013; Saneeyan 2011; Sykora 2005; Szajewska 2009). Ten studies; had participants with a variety of infections (Contardi 1991; Destura unpublished; Fox 2015; Georgieva unpublished; Jirapinyo 2002; Ruszczynski 2008; Shan 2013; Szymanski 2008; Tankanow 1990; Vanderhoof 1999). Studies limited to *H. pylori* infections showed a statistically significant effect (RR 0.32; 95% CI 0.17 to 0.63) as did those limited to respiratory infections (RR 0.46; 95% CI 0.31 to 0.68) as well as mixed infections (RR 0.40; 95% CI 0.23 to 0.71). A test for interaction was not statistically significant (P = 0.66).

Industry Sponsorship

Twelve studies clearly reported on study sponsorship or funding. Of these, seven studies were funded by industry (Correa 2005; Destura unpublished; Merenstein 2009; Ruszczynski 2008; Sykora 2005; Tankanow 1990; Vanderhoof 1999) and 5 were not (Conway 2007; Fox 2015; Saneeyan 2011; Szajewska 2009; Szymanski 2008). Industry sponsored studies showed statistically significant effects (RR 0.59; 95% CI 0.40 to 0.86) as did non-industry sponsored studies (RR 0.32; 95% CI 0.11 to 0.96). A test for interaction between these two groups was not statistically significant (P = 0.31).

Inpatient versus Outpatient

Eighteen studies clearly delineated whether or not their populations were inpatient or outpatient. Eight studies were conducted in an outpatient setting (Benhamou 1999; Correa 2005; Fox 2015; Merenstein 2009; Saneeyan 2011; Tankanow 1990; Vanderhoof 1999; Conway 2007). Five studies were conducted amongst inpatient populations (Georgieva unpublished; Shan 2013; Zheng 2012; Jirapinyo 2002; Szajewska 2009). Five studies had mixed inpatients and outpatient populations (Arvola 1999; Kotowska 2005; Ruszczynski 2008; Szymanski 2008; Destura unpublished). Outpatient studies showed a non-statistically significant effect (RR 0.58; 95% CI 0.34 to 1.02) and inpatient studies showed a statistically significant effect (RR 0.38; 95% CI 0.26 to 0.55). A test for interaction between in and outpatient trials was not statistically significant (P = 0.20).

Single strain versus Multi-strain

Of the 22 studies reporting on incidence of diarrhea, 11 used a single strain (Arvola 1999; Szajewska 2009, Vanderhoof 1999; LaRosa 2003; Benhamou 1999; Erdeve 2004; Kotowska 2005; Shan 2013; Destura unpublished; Georgieva unpublished; Sykora 2005), four used two strains (Tankanow 1990; Jirapinyo 2002; Correa 2005; Zheng 2012), three used three strains (Ruszczynski 2008; Szymanski 2008; Fox 2015), one used four strains (Conway 2007), two used seven strains (Saneeyan 2011; Kodadad 2013), and one used 10 strains (Merenstein 2009). Single strain probiotics showed a statistically significant effect (RR 0.41; 95% CI 0.28 to 0.62), as did multi-strain probiotics (RR 0.52; 95% CI 0.35 to 0.77). A test for interaction between these two groups was not statistically significant (P = 0.44).

SENSITIVITY ANALYSES

Random- versus fixed-effect

A sensitivity analysis using random (RR 0.46; 95% CI 0.35 to 0.61) versus fixed-effect models (RR 0.44; 95% CI 0.37 to 0.53) for the incidence of diarrhea, indicated limited differences between the risk ratio and corresponding 95% confidence intervals. Nonetheless, because the I^2 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 4529 pediatric participants originally randomized in the 22 trials reporting on the primary outcome (incidence of diarrhea). Sixteen of 22 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. 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 analysis (60% of children loss

to follow-up in probiotic group and 20% loss to follow-up in the control group had diarrhea) resulted in a smaller but still statistically and clinically significant effect of intervention (RR 0.69; 95% CI 0.54 to 0.89, I^2 = 63%). In this sensitivity analysis, the pooled incidence of AAD in the probiotic group was 14% compared to 19% in the active, placebo or no treatment control group.

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 decided that a 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 16 trials that did report adverse events, the proportion of adverse events was 3.1% (39/1241) in the treatment group and 42/1214 (3.5%) in the control group. For trials that reported LTFU, we assigned the same adverse event rate as those followed up in their respective randomization groups (3.1% and 3.5% assumed to have adverse events among treatment and control groups respectively) to those who were LTFU. Our primary available case harms analysis (RD 0.00; 95% CI -0.01 to 0.01) yielded the same pooled estimate as the same event rate assumptions analysis (RD 0.00; 95% CI -0.01 to 0.01).

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 Figure 4 and Figure 5). Because of the heterogeneity in our sample (Tau^2 = 0.21), we followed recently proposed guidelines and chose not to run statistical tests of publication bias such as Egger's regression test (Sterne 2011).

Figure 4. Funnel plot of comparison: 1 any specific probiotic versus control (placebo, active or no treatment), outcome: 1.6 Incidence of Diarrhea: Complete case - fixed effects

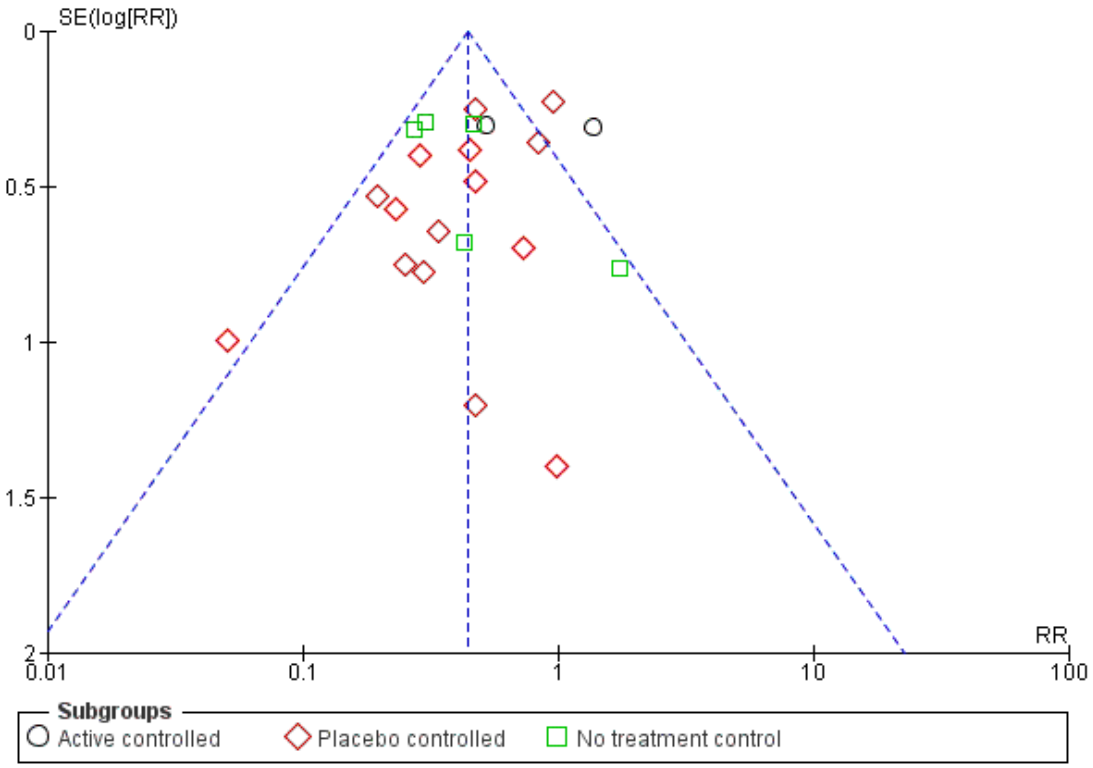
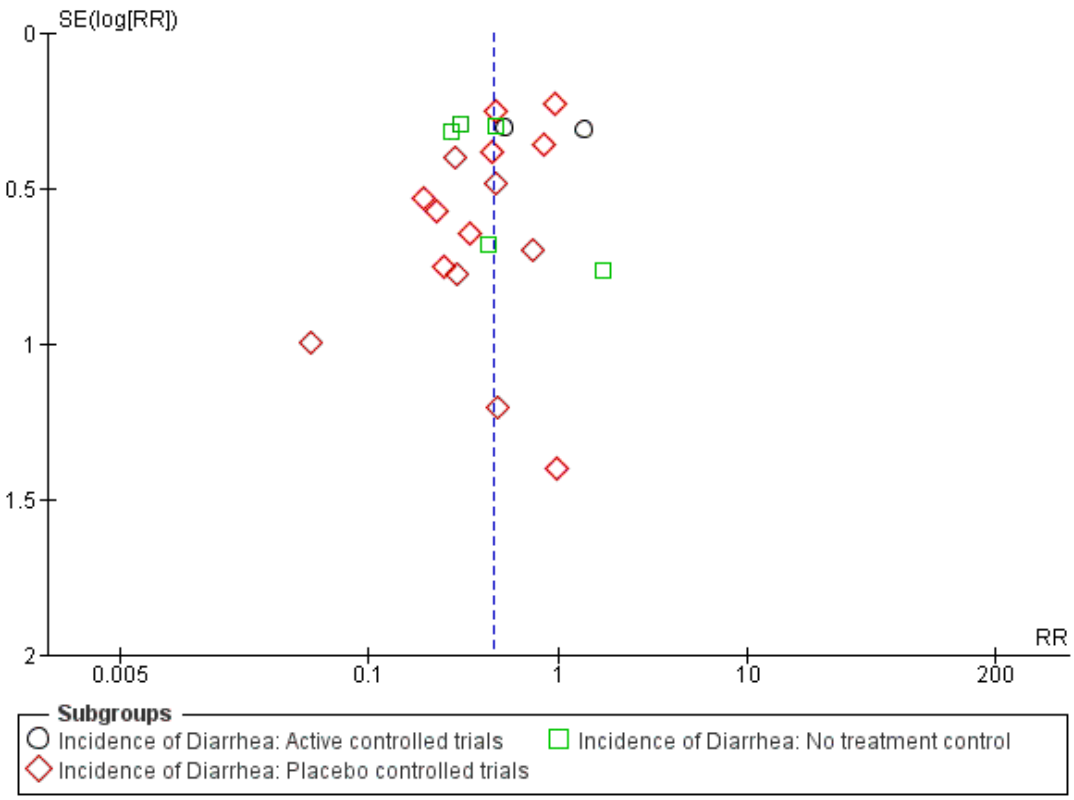


Figure 5. Funnel plot of comparison: 1 Probiotics versus control, outcome: 1.1 Incidence of diarrhea: Complete case.



DISCUSSION

The primary objective of this review was to determine if the co-administration of probiotics with antibiotics prevents or ameliorates AAD in children. Twenty-three eligible studies included treatment with *Bacillus spp., Bifidobacterium spp., Clostridium butyricum, Lactobacilli spp., Lactococcus spp., Leuconostoc cremoris, Saccharomyces spp.,* or *Streptococcus spp.,* alone or in combination. Eight of 23 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 22/23 trials reporting on the incidence of diarrhea, demonstrated a precise benefit from probiotics with an incidence of AAD of 8% compared to 19% in the control groups (RR 0.46; 95% CI 0.35 to 0.61, I^2 = 55%). The number needed to treat (NNT) to prevent one case of diarrhea is ten (NNT 10; 95% CI 8 to 12).

To test the robustness of our available case analysis, we elected to make assumptions about the missing outcome data which were extreme but arguably plausible. Sixteen of 22 trials which reported on our primary outcome reported LTFU (range 2% to 28%). After imputing data for the missing responses, an extreme-plausible analysis (60% of children loss to follow-up in probiotic group and 20% loss to follow-up in the control group had diarrhea) still indicated a statistically and clinically significant benefit for probiotics (4529 participants; RR 0.69; 95% CI 0.54 to 0.89; I^2 = 63%).

Statistical heterogeneity was moderate. 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), and definition of diarrhea. We also conducted *post hoc* subgroup analyses which included diagnosis type, industry sponsorship, inpatient versus outpatient, and single versus multi strain interventions A test for heterogeneity was significant for one subgroup - definition of diarrhea - which may explain some of the statistical heterogeneity. In the previous version of this review high versus low dose probiotics (over or un-

der 5 billion CFU/day) also had a statistically significant test for interaction. With the addition of seven new trials in this update this test for interaction was not statistically significant (P = 0.05), although higher doses were associated with larger effect sizes in our meta-regression (p < 0.001). Using 11 criteria to evaluate the credibility of the subgroup analysis, the results indicate that the subgroup effect based on definition of diarrhea was convincing (Sun 2010); see Appendix 1). This supports the importance of using consistent and clear definitions of diarrhea in clinical trials. This would reduce heterogeneity in future evidence synthesis. Alternatively, researchers could present their results using various definitions (e.g. Fox 2015), while also clearly stating their primary outcome definition in a study protocol to avoid bias.

Regarding safety, 16/23 trials reported on adverse events, and no trials reported any serious adverse events. 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 0.01).

The quality of evidence for each outcome was determined using the GRADE criteria (Guyatt 2008). For the main efficacy outcome, incidence of diarrhea, the quality of evidence was categorized as *moderate* (the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different) because of substantial heterogeneity which we were unable to explain completely with our *a priori* or *post hoc* analyses. 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 attributable to probiotics 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 I^2 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 23 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 Georgieva 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 subgroups (e.g. 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 some limitations. First, 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. Second, 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). To assess differences that may exist between species and strains, we conducted subgroup analyses. Third, our findings are based on an aggregate data meta-analysis and this does not allow us to fully explore patient and intervention level variables that may be associated with AAD. For example, we recently completed a prospective cohort study of 88 children at a large pediatric teaching hospital indicating that children exposed to 3 or more antibiotics are at the highest risk of AAD (34% vs 8%, p<0.01). To explore this issue in meta-analysis, one would require individual patient data which we do not currently have access to.

AUTHORS' CONCLUSIONS

Implications for practice

Moderate quality evidence suggests a protective effect of probiotics in preventing AAD. Our pooled estimate suggests a precise (RR 0.46; 95% CI 0.35 to 0.61) probiotic effect with a NNT of 10. Among the various probiotics evaluated, evidence suggests that *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 among otherwise healthy children, 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 overall quality of the evidence for the primary endpoint of incidence of diarrhea was moderate. We rated the quality of evidence down due to substantial clinical heterogeneity which, for the most part, we were unable to explain via subgroup analyses. More refined trials are needed that test single or multiple strain specific probiotics among outpatients on oral antibiotics and inpatients on intravenous antibiotics. Trials are also needed to assess the safety of probiotics among immune-compromised children. Trials should define potential adverse events *a priori* and monitor for these adverse reactions according to available guidelines (Ioannidis 2004). Finally, 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.

ACKNOWLEDGEMENTS

We would like to thank John K MacDonald (Cochrane IBD/FBD Review Group) for his excellent ongoing support and our translators: Nancy Santesso (Italian), Chian-Yi Liu (Chinese), Alonso Carrasco Labra (Spanish), and Behnam Sadeghirad (Farsi). We wish to thank Jennifer Beardsley and Linda Tally at the Bastyr University Library for designing the grey literature search and helping procure full text articles for review.

Funding for the IBD/FBD Review Group (September 1, 2010 - August 31, 2015) has been provided by the Canadian Institutes of Health Research (CIHR) Knowledge Translation Branch (CON - 105529) and the CIHR Institutes of Nutrition, Metabolism and Diabetes (INMD); and Infection and Immunity (III) and the Ontario Ministry of Health and Long Term Care (HLTC3968FL-2010-2235).

Miss Ila Stewart has provided support for the IBD/FBD Review Group through the Olive Stewart Fund.

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, et al. Prophylactic Lactobacillus GG reduces antibiotic-associated diarrhea in children with respiratory infections: a randomized study. *Pediatrics* 1999;**104**(5):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**(4):163–8.

Contardi 1991 *{published data only}*
Contardi I. Oral bacterial therapy in prevention of antibiotic-induced diarrhea in childhood [Batterioterapia orale quale prevenzione della diarrea da antibiotici in eta pediatrica]. *Clinica Terapeutica* 1991;**136**(6):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**(545):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**(5):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. unpublished.

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**(4):234–6.

Fox 2015 *{published data only}*
Fox, M, Ahuja, K, Robertson, I, Ball, M, Eri R. Can probiotic yogurt prevent diarrhoea in children on antibiotics? A double blind,randomised, placebo-controlled study. *BMJ Open* 2015;**5**:e006474.

Georgieva unpublished *{unpublished data only}*
* Georgieva M, Pancheva R, Rasheva N, Usheva N, Ivanova L, Koleva K. Use of the probiotic *Lactobacillus reuteri* DSM 17938 in the prevention of antibiotic-associated infections in hospitalized Bulgarian children: a randomized, controlled trial. unpublished.

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.

Kodadad 2013 *{published data only}*

Khodadad, A, Farahmand, F, Najafi, M, Shoaran, M. Probiotics for the Treatment of Pediatric Helicobacter Pylori Infection:A Randomized Double Blind Clinical Trial. *Iran J Pediatr* Feb 2013;**23**(1):79–84.

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**(5):583–90.

LaRosa 2003 *{published data only}*

LaRosa M, Bottaro G, Gulino N, Gambuzza F, Di Forti F, Ini G, et al. Prevention of antibiotic-associated diarrhea with Lactobacillus sporogens and fructo-oligosaccharides in children: A multicentric double-blind vs placebo study. *Minerva Pediatrica* 2003;**55**(5):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**(8):750–4.

Ruszczynski 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**(1):154–61.

Saneeyan 2011 *{published data only}*

Saneeyan H, Layegh S, Rahimi H. Effectivness of probiotic on treatment of Helicobacter pylori infection in children. *Journal of Isfahan Medical School* 2011;**29**(146):882–889.

Shan 2013 *{published data only}*

Shan, L, Hou, Z, Wang, F, Liu, N, Chen, L, Shu, H, Zhang, X, Han, X, Cai, X, Shang, Y, Vandenplas, Y. Prevention and treatment of diarrhoea with Saccharomyces boulardii in children with acute lower respiratory tract infections. *Beneficial Microbes* Dec 2013;**4**(4):329–334.

Sykora 2005 *{published data only}*

Sykora J, Valeckova K, Amlerova J, Siala K, Dedek P, Watkins S, et al. 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**(8):692–8.

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**(4):431–6.

Szymanski 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**(1):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**(4):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**(5):564–8.

Zheng 2012 *{published data only}*

Zheng YJ, Mao ZQ, Wu QB, Liu CY, Huang ZH, Huang YK, et al. Multicenter, randomized, controlled clinical trial on preventing antibiotic-associated diarrhea in children with pneumonia using the live *Clostridium butyricum* and *Bifidobacterium* combined powder. *Zhonghua er ke za zhi. Chinese Journal of Pediatrics* 2012;**50**:732–6.

References to studies excluded from this review

Adam 1977 *{published data only}*

Adam J, Barret A, Barret-Bellet C. [Essais cliniques controles en double insu de l'ultra–levure lyphilisee: etude multicentrique par 25 medicins de 388 cas]. *Gaz Med Fr* 1977;**84**:2072–8.

Beausoleil 2007 *{published data only}*

Beausoleil M, Fortier N, Guénette S, L'ecuyer A, Savoie M, Franco M, et al. 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**(11):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**(3):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**(4):PI19–22.

Chapoy 1985 *{published data only}*

Chapoy P. Treatment of acute infantile diarrhea: controlled trial of Saccharomyces boulardii [Traitement des diarrhees

aigues infantiles: essai controle de Saccharomces boulardii]. *Annales de Pédiatrie* 1985;**32**(6):561–3.

Contreras 1983 *{published data only}*
Contreras G, Corti C, Cassani E. Lactobacillus acidophilus in childhood diarrhea. *Compend Invest Clin Latinoam* 1983; **3**:114–116.

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. *Pediatria Polska* 2006;**81**(5):334–41.

Dajani 2013 *{published data only}*
Dajani AI, Abu Hammour AM, Yang DH, Chung PC, Nounou MA, Yuan KY, Zakaria MA, Schi HS. Do probiotics improve eradication response to Helicobacter pylori on standard triple or sequential therapy?. *Saudi J Gastroenterol* 2013 May–Jun;**19**(3):113–120.

Daschner 1979 *{published data only}*
Daschner F, Kienitz M. A saccharomyces preparation for diarrhea? [Perenterol bei Durchfallen?]. *Gynakol Prax* 1979; **3**(3):530–531.

Duman 2005 *{published data only}*
Duman DG, Bor S, Ozütemiz O, Sahin T, O ğ uz D, Itan F, Vural T, Sandkci M, Iksal F, Simek I, Soytürk M, Arslan S, Sivri B, Soykan I, Temizkan A, Bek F, Kaymako ğ lu S, Kalayc C. Efficacy and safety of Saccharomyces boulardii in prevention of antibiotic-associated diarrhoea due toHelicobacterpylori eradication. *Eur J Gastroenterol Hepatol* 2005 Dec;**17**(12):1357–1361.

Erdeve 2005 *{published data only}*
Erdeve O, Tiras U, Dallar Y, Savas S. Saccaromyces boulardii and antibiotic-assoiciated diarrhoea in children. *Alimentary Pharmacology and Therapeutics* 2005;**21**(12):1508–9.

Guandalini 1988 *{published data only}*
Guandalini S, Fasano A. Antibiotic-induced diarrhea. *Rivista Italiana di Pediatria* 1988;**14**(2):145–149.

Honeycutt 2007 *{published data only}*
Honeycutt TC, El Khashab M, Wardrop RM 3rd, McNeal-Trice K, Honeycutt AL, Christy CG, et al. Probiotic administration and the incidence of nosocomial infection in pediatric intensive care: a randomized placebo-controlled trial. *Pediatric Critical Care Medicine* 2007;**8**(5):452–8.

Hosjak 2010 *{published data only}*
Hojsak I, Abdovi ć S, Szajewska H, Milosevi ć M, Krznari ć Z, Kolacek S. Lactobacillus GG in the prevention of nosocomial gastrointestinal and respiratory tract infections. *Pediatrics* 2010 May;**125**(5):e1171–1177.

Hurduc 2009 *{published data only}*
Hurduc V, Plesca D, Dragomir D, Sajin M, Vandenplas Y. A randomized, open trial evaluating the effect of Saccharomyces boulardii on the eradication rate of Helicobacter pylori infection in children. *Acta Paediatr* 2009;**98**(1):127–131.

Imase 2008 *{published data only}*
Imase K, Takahashi M, Tanaka A, Tokunaga K, Sugano H, Tanaka M, Ishida H, Kamiya S, Takahashi S. Efficacy of Clostridium butyricum preparation concomitantly with Helicobacter pylori eradication therapy inrelation to changes in the intestinal microbiota. *Microbiol Immunol* 2008 Mar;**52**(3):156–161.

Kim 2008 *{published data only}*
Kim MN, Kim N, Lee SH, Park YS, Hwang JH, Kim JW, et al. The effects of probiotics on PPI-triple therapy for Helicobacter pylori eradication. *Helicobacter* 2008;**13**(4): 261–8.

Kleinkauf 1959 *{published data only}*
Kleinkauf, I. The use of resistant acidophilus strains during antibiotic therapy [Erfahrungen mit der Anwendung resistenter Acidophilusstämme während der antibiotischen Therapie]. *Arch Kinderheilk* 1959;**160**:51–60.

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** (1):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** (3):246–53.

Lin 2009 *{published data only}*
Lin JS, Chiu YH, Lin NT, Chu CH, Huang KC, Liao KW, Peng KC. Different effects of probiotic species/strains on infections in preschool children: A double-blind, randomized,controlled study. *Vaccine* 2009 Feb 11;**27**(7): 1073–1079.

Lionetti 2006 *{published data only}*
Lionetti E, Miniello VL, Castellaneta SP, Magistá AM, de Canio A, Maurogiovanni G, et al. 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**(10):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**(6):262–3.

Michail 2011 *{published data only}*
Michail S, Kenche H. Gut microbiota is not modified by Randomized, Double-blind, Placebo-controlled Trial of VSL#3 in Diarrhea-predominant Irritable Bowel Syndrome. *Probiotics Antimicrob Proteins* 2011 Mar;**3**(1):1–7.

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 [Valutazione clinica di un

nuovo batterioterapico orale in pazienti di eta pediatrica con dirrea acuta]. *Minerva Medica* 1996;**87**(11):545–50.

Morrow 2010 *{published data only}*
Morrow LE, Kollef MH, Casale TB. Probiotic prophylaxis of ventilator-associated pneumonia: a blinded, randomized, controlled trial. *Am J Respir Crit Care Med* 2010 Oct 15; **182**(8):1058–1064.

Nista 2004 *{published data only}*
Nista EC, Candelli M, Cremonini F, Cazzato IA, Zocco MA, Franceschi F, Cammarota G, Gasbarrini G, Gasbarrini A. Bacillus clausii therapy to reduce side-effects of anti-Helicobacter pylori treatment: randomized, double-blind, placebo controlled trial. *Aliment Pharmacol Ther* 2004 Nov 15;**20**(10):1181–1188.

Pancheva 2009 *{published data only}*
Pancheva R, Stoeva K, Georgieva M, Bliznakova D, Gylybova M, Ivanova L, et al. A randomized controlled trial on the effect of a combination of lactobacillus acidophilus, lactobacillus delbruecki subsp. bulgaricus and bifidobacterium bifidumin the prophylaxis of vomiting and diarrhoea of hospitalised children 1 to 7 years of age. *J Pediatr Gastroenterol Nutr* 2009;**48**(Suppl 3):E111.

Parfenov 2005 *{published data only}*
Parfenov AI, Ruchkina IN, Tsaregorodtsev TM, Serova TI. Clinical efficacy of Actimel for patients with the irritated bowel syndrome with prevailing diarrhea. *Eksp Klin Gastroenterol* 2005;**5**:45–52.

Park 2007 *{published data only}*
Park SK, Park DI, Choi JS, Kang MS, Park JH, Kim HJ, Cho YK, Sohn CI, Jeon WK, Kim BI. The effect of probiotics on Helicobacter pylori eradication. *Hepatogastroenterology* 2007 Oct–Nov;**54**(79):2032–2036.

Penna 2009 *{published data only}*
Penna FGC, Loures MD, de Carvalho AB, Pimenta JR, Figueiredo PCP, Filho LAP, et al. Lack of effect of Lactobacillus delbrueckii H2B20 in the prevention of diarrhea in children hospitalized for short period [La falta de efecto de Lactobacillus delbrueckii H2B20 en la prevención de la diarrea en niños hospitalizados a corto plazo]. *Pediatria (São Paulo)* 2009;**31**:76–80.

Plewinska 2006 *{published data only}*
Plewińska EM, Płaneta-Małecka I, Bąk-Romaniszyn L, Czkwianianc E, Małecka-Panas E. Probiotics in the treatment of Helicobacter pylori infection in children. *Gastroenterologia Polska* 2006;**13**:315–319.

Saavedra 1994 *{published data only}*
Saavedra NA, Oung I, Perman JA, Yolken RH. Feeding of Bifidobacterium bifidum and Streptococcus thermophilus to infants in hospital for prevention of diarrhoea and shedding of rotavirus. *Lancet* 1994;**344**(8929):1046–1049.

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

Schrezenmeir 2004 *{published data only}*
Schrezenmeir J, Heller K, McCue M, Llamas C, Lam W, Burow H, et al. Benefits of oral supplementation with and without synbiotics in young children with acute bacterial infections. *Clinical Pediatrics* 2004;**43**(3):239–49.

Seki 2003 *{published data only}*
Seki H, Shiohara M, Matsumura T, Miyagawa N, Tanaka M, Komiyama A, et al. Prevention of antibiotic-associated diarrhea in children by Clostridium butyricum MIYAIRI. *Pediatrics International* 2003;**45**(1):86–90.

Siitonen 1990 *{published data only}*
Siitonen S, Vapaatalo H, Salminen S, Gordin A, Saxelin M, Wikberg R, et al. Effect of Lactobacillus GG yoghurt in prevention of antibiotic associated diarrhoea. *Annals of Medicine* 1990;**22**(1):57–9.

Simakachorn 2011 *{published data only}*
Simakachorn N, Bibiloni R, Yimyaem P, Tongpenyai Y, Varavithaya W, Grathwohl D, Reuteler G, Maire JC, Blum S, Steenhout P, Benyacoub J, Schiffrin EJ. Tolerance, safety, and effect on the faecal microbiota of an enteral formula supplemented with pre- andprobiotics in critically ill children. *J Pediatr Gastroenterol Nutr* 2011 Aug;**53**(2): 174–181.

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**(2):171–3.

Szajewka 2001 *{published data only}*
Szajewska H, Kotowska M, Mrukowicz JZ, Armańska M, Mikołajczyk W. Efficacy of Lactobacillus GG in prevention of nosocomial diarrhea in infants. *J Pediatr* 2001 Mar;**138**(3):361–365.

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**(9):883–9.

Tolone 2012 *{published data only}*
Tolone S, Pellino V, Vitaliti G, Lanzafame A, Tolone C. Evaluation of Helicobacter Pylori eradication in pediatric patients by triple therapy plus lactoferrin and probioticscompared to triple therapy alone. *Ital J Pediatr* 2012 Oct 31;**38**:63.

Valsecchi 2014 *{published data only}*
Valsecchi C, Marseglia A, Montagna L, Tagliacarne SC, Elli M, Licari A, Marseglia GL, Castellazzi AM. Evaluation of the effects of a probiotic supplementation with respect to placebo on intestinal microflora andsecretory IgA production, during antibiotic therapy, in children affected by recurrent airway infections and skinsymptoms. *J Biol Regul Homeost Agents* 2014 Jan–Mar;**28**(1):117–124.

Wanke 2012 *{published data only}*
Wanke M, Szajewska H. Lack of an effect of Lactobacillus reuteri DSM 17938 in preventing nosocomial diarrhea in

children: arandomized, double-blind, placebo-controlled trial. *J Pediatr* 2012 Jul;**161**(1):40–43.

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**(1):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**(2):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**(4):230–3.

Zhao 2014 ***{published data only}***
Zhao HM, Ou-Yang HJ, Duan BP, Xu B, Chen ZY, Tang J, You JY. Clinical effect of triple therapy combined with Saccharomyces boulardii in the treatment of Helicobacter pyloriinfection in children. *Zhongguo Dang Dai Er Ke Za Zhi* 2014 Mar;**16**(3):230–233.

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**(5):418–35.

Additional references

Akl 2009
Akl EA, Briel M, You JJ, Lamontagne F, Gangji A, Cukierman-Yaffe T, et al. 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**(10):531–4.

Berrington 2004
Berrington A, Borriello SP, Brazier J, Duckworth G, Foster K, Freeman R, et al. 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, et al. Oral probiotics prevent necrotizing enterocolitis in very low birth weight neonates. *Journal of Pediatrics* 2005;**147**(2):192–6.

Borriello 2003
Borriello SP, Hammes WP, Holzapfel W, Marteau P, Schrezenmeir J, Vaara M, et al. Safety of probiotics that contain lactobacilli or bifidobacteria. *Clinical Infectious Diseases* 2003;**36**(3):775–80.

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

Cremonini 2002
Cremonini F, Di Caro S, Nista EC, Bartolozzi F, Capelli G, Gasbarrini G, et al. Meta-analysis: the effect of probiotic administration on antibiotic-associated diarrhoea. *Alimentary Pharmacology and Therapeutics* 2002;**16**(8): 1461–7.

Cunningham-Rundles 2000
Cunningham-Rundles S, Ahrne S, Bengmark S, Johann-Liang R, Marshall F, Metakis L, et al. Probiotics and immune response. *American Journal of Gastroenterology* 2000;**95**(1 Suppl):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**(7350):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**(2):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**(2):455–63.

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**(5): 364–6.

Gibson 1998
Gibson GR. Dietary modulation of the human gut microflora using prebiotics. *British Journal of Nutrition* 1998;**80**(4):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**(2):259–75.

Gogate 2005
Gogate A, De A, Nanivadekar R, Mathur M, Saraswathi K, Jog A, et al. 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**(6):518–24.

Goldin 1998
Goldin BR. Health benefits of probiotics. *British Journal of Nutrition* 1998;**80**(4):S203–7.

Guyatt 2008
Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schünemann HJ, et al. What is "quality of evidence" and why is it important to clinicians?. *BMJ* 2008;**336**(7651): 995–8.

Hammerman 2006
Hammerman C, Bin-Nun A, Kaplan M. Safety of probiotics: comparison of two popular strains. *BMJ* 2006; **333**(7576):1006–8.

Hartling 2009
Hartling L, Ospina M, Liang Y, Dryden DM, Hooton N, Krebs Seida J, et al. 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, et al. Meningitis caused by bifidobacterium in an infant. *Pediatric Infectious Disease Journal* 1988;**7**(9): 669–71.

Hempel 2011
Hempel S, Newberry S, Ruelaz A, Wang Z, Miles JN, Suttorp MJ, Johnsen B, Shanman R, Slusser W, Fu N, Smith A, Roth B, Polak J, Motala A, Perry T, Shekelle PG. Safety of probiotics used to reduce risk and prevent or treat disease. *Evid Rep Technol Assess* 2011;**200**:1–645.

Higgins 2003
Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327** (7414):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**(7211):670–4.

Ioannidis 2004
Ioannidis JP, Evans SJ, Gøtzsche PC, O'Neill RT, Altman DG, Schulz K, et al. Better reporting of harms in randomized trials: an extension of the CONSORT statement. *Annals of Internal Medicine* 2004;**141**(10): 781–8.

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**(4): 377–83.

Johnston 2010
Johnston BC, Shamseer L, da Costa BR, Tsuyuki RT, Vohra S. Measurement issues in trials of pediatric acute diarrheal diseases: a systematic review. *Pediatrics* 2010;**126** (1):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**(2): 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**(1):178–81.

Lin 2005
Lin HC, Su BH, Chen AC, Lin TW, Tsai CH, Yeh TF, et al. Oral probiotics reduce the incidence and severity of necrotizing enterocolitis in very low birth weight infants. *Pediatrics* 2005;**115**(1):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**(5):290–2.

Madsen 2001
Madsen KL. The use of probiotics in gastrointestinal disease. *Canadian Journal of Gastroenterology* 2001;**15**(12):817–22.

McFarland 1998
McFarland LV. Epidemiology, risk factors and treatments for antibiotic-associated diarrhea. *Digestive Diseases* 1998; **16**(5):292–307.

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**(4):812–22.

McFarland 2008
McFarland LV. Antibiotic-associated diarrhea: epidemiology, trends and treatment. *Future Microbiology* 2008;**3**(5):563–78.

McFarland 2010
McFarland LV. Systematic review and meta-analysis of Saccharomyces boulardiiin adult patients. *World Journal of Gastroenterology* 2010;**16**(18):2202–22.

Owens 2008
Owens RC Jr, 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, Bardonnet K, Vagner O, Koenig H. Are live saccharomyces yeasts harmful to patients?. *Lancet* 1999;**353**(9167):1851–2.

Rautio 1999
Rautio M, Jousimies-Somer H, Kauma H, Pietarinen I, Saxelin M, Tynkkynen S, et al. Liver abscess due to a Lactobacillus rhamnosus strain indistinguishable from L. rhamnosus strain GG. *Clinical Infectious Diseases* 1999;**28** (5):1159–60.

Roberfroid 1998
Roberfroid MB. Prebiotics and synbiotics: concepts and nutritional properties. *British Journal of Nutrition* 1998;**80** (4):S197–202.

Saavedra 1999
Saavedra JM. Probiotics plus antibiotics: regulating our bacterial environment. *Journal of Pediatrics* 1999;**135**(5): 535–7.

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

Salminen 2004

Salminen MK, Rautelin H, Tynkkynen S, Poussa T, Saxelin M, Valtonen V, et al. Lactobacillus bacteremia, clinical significance, and patient outcome, with special focus on probiotic L. rhamnosus GG. *Clinical Infectious Diseases* 2004;**38**(1):62–9.

Saxelin 1996

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

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**(6):374–82.

Schrezenmeir 2001

Schrezenmeir J, de Vrese M. Probiotics, prebiotics, and synbiotics -- approaching a definition. *American Journal of Clinical Nutrition* 2001;**73**(2 Suppl):361S–4S.

Sterne 2011

Sterne JA, Sutton AJ, Ioannidis JP, Terrin N, Jones DR, Lau J, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ* 2011;**343**:d4002.

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**(5):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**(5):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**(3):367–72.

Turck 2003

Turck D, Bernet JP, Marx J, Kempf H, Giard P, Walbaum O, et al. Incidence and risk factors for of oral antibiotic-associated diarrhea in an outpatient pediatric population. *Journal of Pediatric Gastroenterology and Nutrition* 2003;**37** (1):22–6.

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**(3): 687–703.

Wistrom 2001

Wistrom J, Norrby SR, Myhre EB, Eriksson S, Granstrom G, Lagergren L, et al. Frequency of antibiotic-associated diarrhoea in 2462 antibiotic-treated hospitalized patients: a prospective study. *Journal of Antimicrobial Chemotherapy* 2001;**47**(1):43–50.

References to other published versions of this review

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, Issue 2. [DOI: 10.1002/14651858.CD004827.pub2]

Johnston 2011

Johnston BC, Goldenberg JZ, Vandvik PO, Sun X, Guyatt GH. Probiotics for the prevention of pediatric antibiotic-associated diarrhea. *Cochrane Database of Systematic Reviews* 2011, Issue 11. [DOI: 10.1002/14651858.CD004827.pub3]

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Arvola 1999

Methods	Randomized, placebo-controlled, double-blinded. Withdrawals/loss to follow-up: 48 participants (28.7%) ITT: no Period of follow-up: 3 months
Participants	N = 167 enrolled Diagnosis: (acute RTIs) Country: Finland Setting: Health Care Centers - City of Tampere and Tampere University Hospital Age: 2 weeks to 12.8 yrs (mean 4.5 yrs)
Interventions	Probiotics: Lactobacillus GG (4 billion CFU/day orally over two weeks) Antibiotics: Not specified
Outcomes	ID (treatment 5% versus placebo 16%) MSF (treatment & placebo 4 (2 to 8) MDD (treatment & placebo 5 (3 to 6) Definition of diarrhea: at least 3 watery or loose stools/day for a minimum of 2 consecutive days
Notes	Funding = Not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Lactobacillus GG and placebo capsules were indistinguishable in appearance and taste
Incomplete outcome data (attrition bias) All outcomes	High risk	Withdrawals/loss to follow-up: 48 participants (28.7%)
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias

Benhamou 1999

Methods	Randomized, active-controlled, double-blinded. Withdrawals/loss to follow-up: 163 participants (21%) ITT: no Period of follow-up: length of antibiotic intervention
Participants	N = 779 enrolled Diagnosis: NS Country: France Setting: Community care practices, Age: 1 to 5 years
Interventions	Probiotic: SB (4.5 billion CFU/day) Control: Diosmectite 6 g/day (1 to 2 years), 9 g/day (> 2 years), Antibiotic: not specified
Outcomes	ID (treatment 7.6%, diosmectite 5.5%) Definition of diarrhea: > 3 liquid stools/day
Notes	Funding = Not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Mentioned randomization, otherwise not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as "double blind" without further details
Incomplete outcome data (attrition bias) All outcomes	High risk	Withdrawals/loss to follow-up: 163 participants (21%). The authors do not describe what happened to these patients
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Unclear risk	No funding from industry or other sources mentioned

Contardi 1991

Methods	Randomized, placebo- controlled. Withdrawals/loss to follow-up: 0 participants ITT: not applicable Period of follow-up: NS
Participants	N = 40 enrolled Diagnosis: (URTIs, LRTIs, Dermatological infections) Country: Italy Setting: Private primary care practice Age: 1 month to 3 years
Interventions	Probiotics: LA, BB (3 billion CFU/day for 10 days) Antibiotic: amoxacillin
Outcomes	Mean number of stools (2 treatment versus 2.7 placebo (P < 0.0001)) MSC (2 treatment versus 2.5 placebo (P = 0.008)) Definition of diarrhea: Not reported
Notes	Funding = Not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Manuscript stated, "suddivisi a randon [divided at random]", otherwise not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	High risk	Blinding not used.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Low risk	The study appears to be free of other sources of bias

Conway 2007

Methods	Randomised, controlled trial (3 arms), double-blind Withdrawals/ losses to follow-up: 0 (data provided by authors) ITT: yes, but NA (obtained pediatric data from authors) Period of Follow-up: 12 days
Participants	N = 106 Diagnosis: NS Country: England Setting: rural general practice Age: 1 to 17 years inclusive
Interventions	Probiotics: ST, LA, BA, LD (1 billion CFU bacteria/day). Antibiotics: NS
Outcomes	ID (treatment 10.8% versus control 6.3%) Definition of diarrhea: 3 or more loose or liquid stools on at least 2 consecutive days
Notes	Funding: Industry (medications)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes
Blinding (performance bias and detection bias) All outcomes	High risk	Blinding for the two groups allocated to yoghurts. Third group not blinded. To avoid unit of analysis errors, we combined the yogurt groups and compared against the third group (no treatment control). Given our analysis technique, will consider unblinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Overall, 38 patients were LTFU from the adults and child data combined (n = 12, n = 9, n = 17). It is unclear how many children specifically were lost to follow-up
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Low risk	Acknowledged by authors: Imbalance for previous AAD might have distorted main outcome results

Correa 2005

Methods	Randomized, formula-controlled, double-blinded. Withdrawals/loss to follow-up: 12 ITT: No Period of follow-up: 15 days
Participants	N = 169 enrolled Diagnosis: NS Country: Brasil Setting: Hospital ambulatory care Age: mean 1.8 years
Interventions	Probiotic: BL, ST (approximately 825 million CFU/day) Control: Formula (3.3 g protein, 4.4 g fat, 11.8 g carbohydrates per 100 kcal plus vitamins and minerals) Antibiotics: ampicillin n = 119, amoxicillin n = 101, cephalosporin n = 31, amoxicillin+clavulanic acid n = 16, penicillin n = 10, oxacillin n = 9, others n = 20
Outcomes	ID (treatment 16.3% versus control 31.2%) MDD (treatment 3.92 +/- 2.47 versus control 5.00 +/- 2.80) Definition of diarrhea: 3 or more liquid stools/day for at least 2 consecutive days
Notes	Funding = Industry (Nestle, otherwise unclear re: medications versus operations) and independent

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind: The appearance and odour of the probiotic and nonsupplemented formulas were identical
Incomplete outcome data (attrition bias) All outcomes	Low risk	12 patients dropped out (<10% and relatively even for each group). 7 from probiotic 5 from control. Reasons why are given. However the reasons given were not evenly distributed. Control lost 4 from loss to follow-up while probiotic lost none for that reason. Probiotic lost 5 from insufficient ingestion and control lost none for that reason. However, the minimum amount needed for ingestion was described seemingly *a priori.*

Correa 2005 (*Continued*)

Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Unclear risk	Nestle the maker of the probiotic intervention provided some funding. The report is not co-authored by the company, however there is no clear mention of Nestle's involvement beyond that of providing the product

Destura unpublished

Methods	Randomized, no intervention controlled, open label trial Withdrawals/loss to follow-up: 0 (data provided by authors) ITT: N/A Period of follow-up: until end of antibiotic therapy (7 to 21 days)
Participants	N = 323 Diagnosis: respiratory, genito-urinary, skin and soft tissue infections Country: the Philippines Setting: hospital general care (inpatient and outpatient) Age: treatment 4.1 years and control 4 years (means)
Interventions	Probiotics: BC (4 billion CFU bacteria/day) Antibiotics: Penicillins n = 151, cephalosporin n = 112, coamoxyclav/ampicillin-sulbactam n = 25, other n = 35
Outcomes	ID: 1.85% treatment versus 4.35% control MDD: 4.00 (SD 3.46) treatment versus 3.86 (SD 2.26) control Definition of diarrhea: 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
Notes	Funding: Industry (otherwise unclear re: medications versus operations)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Complete blocks of varying sizes were randomly allocated by a "third party" through a central telephone randomization system
Allocation concealment (selection bias)	Unclear risk	"Complete blocks of varying sizes were randomly allocated by a "third party" through a central telephone randomization system." "Each patient was identified using a center number, a treatment number (provided by the treatment code found in the intervention drug label) and the patient's initials." "

Destura unpublished (*Continued*)

		a research assistant assigned per center kept the randomization plan and only opened it when an eligible patient was entered in the study"
Blinding (performance bias and detection bias) All outcomes	High risk	Blinding not used - open label study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Two patients were lost to follow-up (1 in each arm) after clinical outcomes were measured. So there was no missing outcome data
Selective reporting (reporting bias)	Low risk	Protocol posted on clinicaltrials.gov and results as presented to us by authors match up
Other bias	Low risk	Study funded by industry. Not clear if author is employed by industry but assume so. Also no clear statement regarding industry involvement is trial design. The study appears to be free of other sources of bias

Erdeve 2004

Methods	Randomized, no treatment controlled. Withdrawals/loss to follow-up: 187 participants (28.6%) ITT: no Period of follow-up: NS
Participants	N = 653 enrolled Diagnosis: NS Country: Turkey Setting: Unclear Age: 1 to 15 years
Interventions	Probiotic: SB (5 billion CFU/day) Antibiotics: salbactam-ampicillin n = 234, azithromycin n = 232
Outcomes	ID (treatment 5.7% versus control 18.9%) Definition of diarrhea: Watery stools on 3 or more times on any day of antibiotic treatment
Notes	Funding = Not reported
Risk of bias	

Erdeve 2004 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization not described, however, contact with authors indicated that the trial was randomized
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No mention is made of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	Withdrawals/loss to follow-up: 187 participants (28.6%). There is no mention of which proportion of drop outs were from each group
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Unclear risk	No mention of funding

Fox 2015

Methods	Randomized, placebo-controlled, double-blinded Withdrawals/loss to follow-up: 2 (2.8%) ITT: No Period of follow-up: 1 week after antibiotic treatment ended
Participants	N = 72 Diagnosis: otitis, pharyngitis, chest infections, other Country: Australia Setting: multisite general care Age: Mean age 6.8 years treatment group, 6.3 years control group
Interventions	Probiotic: 2 x 100 gram tubs per day containing; LGG 5.2×10^9 CFU/day, Bb-12 5.9×10^9 CFU/day, La-5 8.3×10^9 CFU/day Antibiotics: Beta lactams n = 64 Macrolides n = 5 Tetracyclines n = 1
Outcomes	ID: 1/34 (2.9%) treatment group vs 21/36 (61.7%) control. P-value = < 0.001 Various definitions of diarrhea. These included: (A) stool consistency $\geq$ 5 and stool frequency $\geq$ 2/day for more than 2 days; (B) stool consistency $\geq$ 5 and stool frequency $\geq$ 3/day for more than 2 days; (C) stool consistency $\geq$ 6 and stool frequency $\geq$ 2/day for more than 2 days; and (D) stool consistency $\geq$ 6 and stool frequency $\geq$ 3/day for more than 2 days

Notes	Funding = Industry provided yogurt but had no input in study design Independent lab assessed the probiotics	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"A statistician generated independent allocation sequences and randomisation lists for each study site, using the random number generator in Microsoft Excel"
Allocation concealment (selection bias)	Low risk	"To ensure allocation concealment, an independent person oversaw packaging and labelling of trial treatments based on the randomisation schedule"
Blinding (performance bias and detection bias) All outcomes	Low risk	"All investigators, participants, outcome assessors and data analysts were blinded to the assigned treatment throughout the study" "The yogurt was in 100 g containers with identical labels. The yogurts were similar in taste but one yogurt was thinner in texture. Participants were only shown the yogurt they were going to use and did not have the opportunity to make a comparison" Patients/parents recorded diarrhea events and AE in diary Participants and parents were blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Two out of 72 randomized patients were lost to follow-up It was not clear from which group they were. However the LTFU number was small and the event spread large LTFU would not significantly affect the diarrhea outcome in a material way LTFU would not significantly affect the composite AE outcome
Selective reporting (reporting bias)	Low risk	Trial was prospectively registered Australian New Zealand Clinical Trials Registry ACTRN12609000281291 The outcomes listed of stool frequency and consistency are compatible with reported outcomes

Other bias	Low risk	The study was supported by Parmalat Australia who had no role in the formulation or conduct of the study or in the data analysis or interpretation

Georgieva unpublished

Methods	Randomized, double-blind trial Withdrawals/Loss to follow-up: 3 (3%) ITT: No Period of follow-up: 21 days following end of antibiotic treatment
Participants	N= 100 Diagnosis: Infections of respiratory, gastrointestinal, pancreas, eyes, ears nose, throat, urinary tracts or systems Country: Bulgaria Setting: hospital admitted patients Age: 3-12 mean 8.85
Interventions	Probiotics: 100 million CFU per day Lactobacillus reuteri DSM 17938 Antibiotics: NS, 1-3
Outcomes	ID: Control 1 versus Treatment 1 Definition of diarrhea: An episode of diarrhoea was defined as three or more (≥3) soft and unformed or watery bowel movements per day for at least 48 hours
Notes	Funding: NS

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Computer generated randomization list of case numbers"
Allocation concealment (selection bias)	Low risk	Participants entered consecutively starting with the lowest case number in each stratum Randomisation and labelling of the test-samples were made by an independent physician
Blinding (performance bias and detection bias) All outcomes	Low risk	Study described as double blind Diarrhea-diary/ and Bristol scale filled out by parents/children both of whom were blind AE- It appears GSRS symptom score filled

Georgieva unpublished (*Continued*)

		out by parents/children or study physicians both of whom were blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Diarrhea - 3% missing outcome data It is unclear which group they were from. While the total number missing is low the total number of diarrhea events was also low. The missing outcome data could bias the results in a material way. AE-Based on their reported results in the manuscript there were no reported AE although they also report GSRS symptom scale. We were not able to reach the authors to clarify this. Assuming no AE than even the low missing outcome data could materially bias the results for this outcome
Selective reporting (reporting bias)	Low risk	Manuscript outcomes the same as a priori listed in clinicaltrials.gov
Other bias	Unclear risk	This is an unpublished trial. Funding was not reported and they did not respond to email inquiry

Jirapinyo 2002

Methods	Randomized, placebo-controlled, double-blinded. Withdrawals/loss to follow-up: 0 participants ITT: Not applicable Period of follow-up: Not provided	
Participants	N = 18 enrolled Diagnosis (Meningitis and/or Sepsis) Country: Thailand Setting: Single-site hospital inpatients Age: 1 to 36 months	
Interventions	Probiotics: LA, BI (1 capsule orally TID for 7 days, 6 billion CFU per day), Antibiotic: cefprozil n = 16, ampicillin n = 4, gentamycin n = 2, cloxacillin n = 1	
Outcomes	ID (treatment 37.5% versus placebo 80%) Definition of diarrhea: Not reported	
Notes	Funding = Not reported	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Jirapinyo 2002 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Based on a randomization list. Unclear how that was generated
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as "double blind" without further details
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There were no mentions of drop outs. There was mention of 3 cases of sepsis. There was also mention that cases where probiotics sepsis was possible would result in unblinding although it wasn't clear if those three were unblinded. There was no statistical analysis as well.
Selective reporting (reporting bias)	Unclear risk	There is no definition mentioned of diarrhoea. In the methods section they mentioned the "characteristics and frequency" of stools would be observed. In the results section the number of patients with diarrhoea and days of diarrhoea were noted. It is unclear what characteristics means and why they weren't reported.
Other bias	Unclear risk	No mention of funding source

Kodadad 2013

Methods	Randomized, placebo-contolled study, double-blinded Withdrawals/Loss-to-follow-up: 0 (0%) ITT: Not needed Period of follow-up: 7 days (duration of antibiotics and probiotics)
Participants	N = 66 Diagnosis: *H.pylori* Country: Iran Setting: multiple, children's medical center Age: range 3 to 14 years mean 9.09 years
Interventions	Probiotics: 1 billion CFU/1 sachet per day of combination of following species: *Lactobacillus acidophilus*, *Lactobacillus rhamnosus*, *Lactobacillus bulgaricus*, *Lactobacillus casei*, *Streptococcus thermophilus*, *Bifidobacterium infantis* and *Bifidobacterium breve* Antibiotics: Oral amoxicillin 50 mg/kg/day twice daily; oral furazolidone 6 mg/kg/day twice daily, oral omeprazole 1 mg/kg/day (duration: 4 weeks)

Kodadad 2013 (*Continued*)

Outcomes	ID: Control 8 (24.24%) versus Treatment 2 (6.06%) Definition of diarrhea: NS
Notes	Funding: NS

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomized," however researchers did not explain further
Allocation concealment (selection bias)	Unclear risk	Not enough information provided
Blinding (performance bias and detection bias) All outcomes	Low risk	Diarrhea and other AE were reported by parents and patients both of whom were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Outcomes reported in line with outcomes set a priori on register
Other bias	Low risk	Based on registry info it is sponsored by the university of Tehran

Kotowska 2005

Methods	Randomized, placebo-controlled, double-blinded. Withdrawals/loss to follow-up: 23 participants (8.5%) ITT: Yes Period of follow-up: 2 weeks after the end of antibiotic treatment
Participants	N = 269 enrolled Diagnosis: (Bronchitis n = 64, Otitis media n = 79, Pneumonia n = 62, Tonsillitis n = 58, other RTIs n = 6) Country: Poland Setting: Three teaching hospitals (n = 72) and two out-patient clinics (n = 197) Age: 6.2 to 182 months (5 months to 15 years)
Interventions	Probiotic: SB (10 billion CFU/day for duration of antibiotic treatment [range 7 to 9 days] Antibiotics: cefuroxime axetil = 72, amoxicillin clavulanate = 46, amoxicillin = 33, cefuroxime (IV) = 39, penicillin = 33, clarithromycin = 20, roxithromycin = 13, other = 13

Kotowska 2005 (*Continued*)

Outcomes	ID (treatment 7.5% versus placebo 23%) Definition of diarrhea: Greater than or equal to 3 loose or watery stools/day for a minimum of 48 hours, occurring during and/or up to 2 weeks after the end of antibiotic treatment
Notes	Funding = Not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer generated
Allocation concealment (selection bias)	Low risk	To ensure allocation concealment, an independent subject prepared the randomization schedule and oversaw the packaging and labelling of trial treatments
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind: All investigators, participants, outcome assessors and data analysts were blinded to the assigned treatment throughout the study
Incomplete outcome data (attrition bias) All outcomes	Low risk	<10% dropout/lost to follow-up. Dropouts balanced in numbers across intervention groups with similar reasons for missing data across groups. Additionally the authors conducted extreme case scenarios
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Unclear risk	No mention of funding

LaRosa 2003

Methods	Randomized, placebo-controlled, double-blinded. Withdrawals/loss to follow-up: 22 participants (18.3%) ITT: Yes Period of follow-up: Not provided
Participants	N = 120 enrolled Diagnosis: (Pharangitis n = 48, Tonsillitis n = 46, Otitis n = 22, Bronchitis n = 18, Other n = 10 [note some children had more than one infection]) Country: Italy Setting: multi-centered Age: mean 6.6 years

LaRosa 2003 (*Continued*)

Interventions	Probiotic: LS (5.5 billion CFU/day) with Prebiotic: FOS (250 mg/d) for 10 days) Antibiotics: mixture, NS
Outcomes	ID (treatment 29% versus placebo 62%) MDD (0.7 versus 1.6 days (P = 0.002)) Definition of diarrhea: Greater than or equal to 2 liquid stools over 24 hours
Notes	Funding = Not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer generated
Allocation concealment (selection bias)	Low risk	Each patient was given a code. The treatment package corresponded with the code
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, identical placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts balanced in numbers across intervention groups with similar reasons for missing data across groups
Selective reporting (reporting bias)	High risk	Methods section indicate "condizioni generale" [general condition], but outcome not reported
Other bias	Low risk	The study appears to be free of other sources of bias

Merenstein 2009

Methods	Randomized, placebo controlled, double-blinded Withdrawal/loss to follow-up: 8 participants (6.4%) ITT: no Period of follow-up: 15 days
Participants	N = 125 Diagnosis: URI Country: USA Setting: primary care office Age: 2.9 years treatment and 3.2 years control

Merenstein 2009 (*Continued*)

Interventions	Probiotics: LL, LP, LR, LC, LL subspecies diacetylactis, Leuconostoc cremoris, Bifidobacterium longum, BB, LA, SF (at least half of a 150 ml drink containing 7 to 10 billion CFU bacteria and yeast/day) Antibiotics: NS
Outcomes	ID: 18.0% treatment versus 21.9% control Definition of diarrhea: NS
Notes	Funding: Industry (medication and operations)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The randomization scheme was generated using permuted blocks with block size equal to 8
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind: "All research personnel and statisticians were blinded throughout the study, including during initial review of data." A matching placebo was used
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Loss to follow-up was exceptionally low. Only 4 participants in each group were unable to be contacted at the final follow-up on day 15."
Selective reporting (reporting bias)	Low risk	Outcomes identical to that reported in clinicaltrials.gov
Other bias	Low risk	Lifeway foods provided drink and funding although no author was associated with the company

Ruszczynski 2008

Methods	Randomized, placebo-controlled, double blind Withdrawals/loss to follow-up: 0 ITT: yes Period of follow-up: two weeks following end of antibiotic treatment
Participants	N = 240 Diagnosis: Otitis, URT, LRT, UTI, other Country: Poland

	Setting: Two hospitals and one private practice Age: treatment 4.6 years and control 4.5 years
Interventions	Probiotics: Lactobacillus Rhamosus (strains E N, Oxy and Pen) (40 billion CFU bacteria/day) Antibiotics: penicillins = 15, broad spectrum penicillins = 119, cephalosporins = 89, macrolides = 15, clindamycin = 2
Outcomes	ID: (treatment 7.5% versus control 16.7%) Definition of diarrhea: greater than or equal to 3 loose stools per day for a minimum of 48 hours, occurring during and/or up to two weeks after the end of the antibiotic therapy
Notes	Funding: Industry (otherwise unclear re: medications versus operations) and Independent (Medical University of Warsaw)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer generated: Permuted block of six (three received placebo and three, active treatment). Separate randomization lists were prepared for each site
Allocation concealment (selection bias)	Low risk	To ensure allocation concealment, an independent subject prepared the randomization schedule and oversaw the packaging and labelling of trial treatments
Blinding (performance bias and detection bias) All outcomes	Low risk	All investigators, participants, outcome assessors and data analysts were blinded to the assigned treatment throughout the study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Overall, three of the randomized children (one in the probiotic group and two in the placebo group) discontinued the study intervention and started to use one of the commercially available probiotics products. However, no patient was lost to follow-up
Selective reporting (reporting bias)	Low risk	All primary and secondary outcomes as reported in the methods section were reported on in the results section
Other bias	Low risk	Biomed provided the intervention but they "had no role in the conception, design, or

Ruszczynski 2008 (*Continued*)

		conduct of the study or in the analysis or interpretation of the data"

Saneeyan 2011

Methods	Randomized, placebo-controlled, patient blinded Withdrawals/Loss to follow-up: None ITT: None needed Period of follow-up: NS
Participants	N=50 Diagnosis: *H.pylori* Country: Iran Setting: Community healthcare Age: 4-14 mean 8.2 treatment group, 9.5 control group
Interventions	Probiotics: One sachet per day of 1 billion CFU combined of following species: Lactobasillus casei, Lactobacillus acidophilus, Lactobasillus reuteri, Lactobasillus bulgaricus, Streptococcus, Bifidobacterium bifidum, Bifidobacterium infantis Antibiotics: Amoxicillin 25 mg/kg BID (max dose is 1.5 grams per day), Clarithromycin 10 mg/kg BID (max dose 1 gram per day) Omeprazole 0.5 mg/kg BID (no max dose listed)
Outcomes	ID: 13 Control versus 3 Treatment Definition of diarrhea: 3 times excretion per day or more, if it is loose or watery for at least 48 hours during the therapy or two weeks after the antibiotic therapy
Notes	Funding: grant from university, other sources NS

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random sequence number table (random number generating)
Allocation concealment (selection bias)	Unclear risk	Nothing mentioned
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Sachets (of probiotic and placebo) look the same. Nothing else listed about blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study
Selective reporting (reporting bias)	Unclear risk	All outcomes listed in methods are reported in results. No registered protocol could be found

Saneeyan 2011 (*Continued*)

Other bias	Unclear risk	No funding from industry or other sources mentioned

Shan 2013

Methods	Randomized open trial, nested observational Withdrawals/Loss to follow-up: 50 ITT: No Period of follow-up: 2 weeks following end of antibiotic treatment
Participants	N= 333 Diagnosis: pneumonia, asthma, lower respiratory tract infection Country: China Setting: single site hospital Age: average 48 months
Interventions	Probiotics: Saccharomyces boulardii 2×250 mg (10 billion CFU/day) Antibiotics: cefepime, cefoperazone, sulbactam, cefuroxime, amoxicillin, clavulanic acid, erthromycin
Outcomes	ID: Conrol 42 (29.2%) versus treatment 11 (7.9%) Definition of diarrhea: ≥3 loose or watery stools (BSS type 5, 6 and 7) per day during at least 2 days, occurring during treatment and/ or up to 2 weeks after the antibiotic therapy had stopped. AAD was defined as diarrhoea caused by C. difficile or diarrhoea with negative stool cultures
Notes	Funding: NS

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomisation was done according to a computer-determined allocation to group A or B"
Allocation concealment (selection bias)	Low risk	"The [randomization] sequence was concealed in an envelope, and the next neutral envelope was opened each time the next patient was included in the study"
Blinding (performance bias and detection bias) All outcomes	High risk	"This study was an open, randomised, controlled clinical trial"
Incomplete outcome data (attrition bias) All outcomes	High risk	15% missing outcome data

Selective reporting (reporting bias)	Low risk	Not registered. The outcomes in the methods section match the outcomes in the results section
Other bias	Unclear risk	Funding source unclear. One of the authors is a consultant for a probiotics company

Sykora 2005

Methods	Randomized, double-blind study Withdrawals/Loss to follow-up: 6 ITT: Yes Period of follow-up: 4 weeks
Participants	N= 86 Diagnosis: *H.pylori* Country: Czech Republic Setting: Hospital general care, 3 sites Age: average 12.6 treatment, average 12.9 control
Interventions	Probiotics: Lactobacillus casei DN-114 001, A dose of 100 mL of containing 10 billion CFU/day) Antibiotics: oral amoxicillin 25 mg/kg, oral clarithromycin 7.5 mg/ kg, omeprazole 10 mg (15-30 kg) or 20 mg (30 kg)
Outcomes	ID: Control 5 versus Treatment 3 Definition of diarrhea: not defined; data in adverse events
Notes	Funding: Danone, Ministry of Health of Czech Republic

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomization was performed using a computer generated randomization list"
Allocation concealment (selection bias)	Low risk	"All children received their patient number in ascending order corresponding to the order of inclusion. This number corresponded to a randomized medication scheme"
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind Diarrhea and AE reported by patients, parents, and study personnel all of whom were blinded

Sykora 2005 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	The numbers and reasons for withdrawal/ drop-outs were described and comparable across groups (and ≤ approximately 10%)
Selective reporting (reporting bias)	Low risk	Not registered. The primary outcome of interest was H pylori. However "patients and parents were asked to complete a standard questionnaire to assess the occurrence of prospectively defined adverse events." AE which include our outcome diarrhea were identified a priori
Other bias	Low risk	Sponsor is acknowledged and no one from the sponsoring agency was an author

Szajewska 2009

Methods	Randomized, placebo controlled, double blind Withdrawals/loss to follow-up: 17 (20.9%) ITT: yes Period of follow-up: 3 weeks (2 weeks after end of antibiotic treatment)
Participants	N = 83 Diagnosis: H. pylori infection Country: Poland Setting: hospitalized/inpatients Age: 12.3 years treatment and 11.9 years control
Interventions	Probiotics: Lactobacillus GG (1 billion CFU/day) Antibiotics: all patients received amoxicillin and clarithromycin (all patients also received omeprazole a proton pump inhibitor)
Outcomes	ID: (6% treatment versus 20% control) Definition of diarrhea: 3 or more loose or watery stools per day for a minimum of 48 hours occurring during and/or up to 2 weeks after the end of antibiotic therapy
Notes	Funding: Industry (medications) and Independent (Medical University of Warsaw)

Risk of bias

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

Szajewska 2009 (*Continued*)

Allocation concealment (selection bias)	Low risk	LGG and the control product were packed in identical forms. Randomization codes were secured until all of the data entry was complete
Blinding (performance bias and detection bias) All outcomes	Low risk	All of the study personnel, patients, and personnel involved in the conduct of the study were unaware of treatment assignments throughout the study
Incomplete outcome data (attrition bias) All outcomes	High risk	10 drop outs versus 7 drop outs. Reasons why were given (no diary or UBT). Data was analyzed with opposite extremes of assumptions regarding those drop outs for H. Pylori but not for side effects
Selective reporting (reporting bias)	Low risk	All outcomes mentioned in methods section were reported on in results section
Other bias	Low risk	Baseline characteristics are very close. Dicofarm supplied study product but "had no role in the conception, design, or conduct of the study or in the analysis or interpretation of data"

Szymanski 2008

Methods	Randomized, placebo controlled, double blind Withdrawal/loss to follow-up: 0 ITT: yes Period of follow-up: less than or equal to 4 weeks (2 weeks after end of antibiotic treatment)
Participants	N = 78 Diagnosis: otitis media, respiratory tract infections, scarlet fever, other Country: Poland Setting: pediatric hospitals and outpatient clinics Age: median age 7 years (range 1 to 15 years)
Interventions	Probiotics: *Bifidobacterium longum* PL03, LRKL53A, LP PL02 (200 million CFU bacteria/day) Antibiotics: amoxicillin w/ or w/o clavulanate = 34, cephalosporins = 20, penicillin = 5, macrolides = 18, aminoglycosides = 1
Outcomes	ID: (2.5% treatment versus 5.3% control) MSF: (1.0 +/- 0.4 treatment versus 1.3 +/- 0.6) Definition of diarrhea: 3 or more 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

Szymanski 2008 (*Continued*)

Notes	Funding: Industry (medications)	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer generated
Allocation concealment (selection bias)	Low risk	To ensure allocation concealment, an independent person prepared the randomization schedule and oversaw the packaging and labelling of the trial treatments
Blinding (performance bias and detection bias) All outcomes	Low risk	All study personnel and parents and guardians were unaware of the group assignments. Randomization codes were secured until all data entry was complete
Incomplete outcome data (attrition bias) All outcomes	Low risk	The analysis was based on the intention-to-treat principle, with all patients included in their assigned group. No dropouts reported
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Unclear risk	"The active treatment and placebo used in this study were prepared by IBSS Biomed S.A., Cracow, Poland." No comment was offered with regards to IBSS Biomed's role in study design, analysis

Tankanow 1990

Methods	Randomized, placebo-controlled, double-blinded. Withdrawals/loss to follow-up: 22 participants (36.6%) ITT: no Period of follow-up: Not provided
Participants	N = 60 enrolled Diagnosis: children with infections in which amoxicillin was reasonable therapy Country: United States Setting: Local pediatric practice during a 13 month period Age: 5 months to 6 years (mean age 29+/-17 months)
Interventions	Probiotics: LA, LB ((1 gram packets (500 million per packet) 4 times per day equalling approximately 2 billion CFUs/day) for 5 to 12 days

Tankanow 1990 (*Continued*)

	Antibiotics: amoxicillin only - dose based on clinician experience and manufactures dosing guidelines
Outcomes	ID (treatment 66% versus placebo 69.5%) Definition of diarrhea: one or more abnormally loose bowel movements/day throughout the study period of 1 to 10 days
Notes	Funding = supported in full by Hynson, Westcott & Dunning Products

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomization provided by product manufacturer, otherwise unclear how randomization was generated
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	High risk	Double-blind, otherwise not described. Blinding codes were held by manufacturer. One reason mentioned for subjects not continuing the study was "taste." There was an imbalance of drop outs from groups. Could taste be different for each intervention? Did this affect blinding on the side of the patient? It is unclear how many dropped out for taste reasons
Incomplete outcome data (attrition bias) All outcomes	High risk	There was a 37% drop-out/ lost-to-follow-up. The final number of subjects analyzed was not equal in magnitude (15 active, 23 placebo). The number of subjects who didn't finish the study was high when compared to observed outcomes (22 didn't finish, 26 cases of diarrhoea (10 in active, 16 in placebo)).
Selective reporting (reporting bias)	Low risk	Outcomes mentioned in Methods section were consistent to those mentioned in Results section
Other bias	High risk	Study was funded in full by manufacturer (i.e. provided product and placebo and also provided the randomization and held the codes)

Vanderhoof 1999

Methods	Randomized, placebo-controlled, double-blinded. Withdrawals/loss to follow-up: 14 participants (6.9%) ITT: no Period of follow-up: until antibiotic treatment was completed or diarrhea ceased
Participants	N = 202 enrolled Diagnosis: for children with complete follow-up (Otitis n = 109, Pharangitis n = 37, Bronchitis n = 19, Dermatological n = 11, Sinusitis n = 10, Other n = 2) Country: United States Setting: private pediatric practice Age 4 to 12 yrs (mean age 4 years)
Interventions	Probiotics: LGG (10 billion for children less than 12 kg; 20 billion for greater than or equal to 12 kg for duration of antibiotic treatment (7 to 14 days) Antibiotics: amoxicillin n = 65, amoxicillin clavulanate n = 33, cefprozil n = 13, clarithromycin n = 18, other n = 59
Outcomes	ID (treatment 8% versus control 26%) MDD (4.7 versus 5.9), MSC (5.29 versus 5.04) MSF (1.51 versus 1.59) Definition of diarrhea: Greater than or equal to 2 liquid stools/day on > 2 occasions throughout the study period
Notes	Funding = Industry (operational funds from ConAgra Inc). Author also a consultant for ConAgra

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomized with a computer-generated randomization table
Allocation concealment (selection bias)	Unclear risk	Product randomization by blinded numeric codes was performed by the supplier before the product was shipped to the investigation site. Codes were kept by the supplier until all data were collected
Blinding (performance bias and detection bias) All outcomes	Low risk	The LGG and placebo were packed in identical bottles with identical capsule covers." "Codes were kept by the supplier until all data were collected"
Incomplete outcome data (attrition bias) All outcomes	Low risk	"The study was completed by 188 children (median age 4 years); 14 failed to complete the study, primarily because of antibiotic

Vanderhoof 1999 (*Continued*)

		noncompliance or inability of the investigators to contact the primary caregiver at the assigned follow up time. None of the participants failed to complete the 10-day course of antibiotics because of a change in stool consistency or frequency. There were no failures resulting from untoward effects of either LGG or placebo. Both active and placebo groups were similar for age distribution, sex, and type of antibiotics, and all who completed the study had no difficulty consuming the prescribed amount"
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported
Other bias	Unclear risk	Lead author is a consultant for CAG nutrition (division of ConAgra) which makes the product

Zheng 2012

Methods	Randomized, open-label, no placebo-control Withdrawals/Loss to follow-up: 3 ITT: No Period of follow-up: 7 days
Participants	N= 372 Diagnosis: Pneumonia Country: China Setting: Hospital, in-patient, 7 sites Age: average age in months: 13.99
Interventions	Probiotics: *Clostridium Butyricum* (50 million CFU), *Bifidobacterium* (500 million CFU) 4 packets a day 2.2 billion CFU/day Antibiotics: mixed pencillin, cephalosporin, macrolides
Outcomes	ID: Control 30 (16.8%) versus Treatment 15 (7.8%) Definition of diarrhea: 2 or more BM over the pt amount (they has baseline BM # for each pt. And an increase of 2 or more over that baseline was considered diarrhea)
Notes	Funding: NS

Risk of bias

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

Zheng 2012 (*Continued*)

Random sequence generation (selection bias)	Low risk	Randomized block design. Use SAS software to generate 504 randomized number for the 7 hospital (72 numbers for each center)
Allocation concealment (selection bias)	High risk	Investigator appears to know the randomization schedule when assigning participants
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding procedure was described in the study. Seems to be an open label trial. No mention of blinding. No treatment comparison
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 drop out of unknown reason & 5 exclusion (2 due to incomplete report, 3 due to rotavirus), from total of 380 (drop-out rate 2.1%)
Selective reporting (reporting bias)	Low risk	Their outcome report is consistent with the study protocol. Study is registered at Chinese Ethics Committee of Registering Clinical Trials (http://www.chictrdb.org/)
Other bias	Unclear risk	The probiotic is provided by Shandong Kexing Bioproducts Co.,Ltd. (www.sdkexing.com) No report for study funding

METHODS: Intention- to-treat (ITT), Not specified (NS)
PARTICIPANTS: respiratory tract infection (RTI), upper respiratory tract infection (URTI), lower respiratory tract infection (LRTI), Not specified (NS)
INTERVENTIONS: *Bifidobacteria anamalis subsp. lactus* (BA), *Bifidobacterium breve* (BB), *Bacillus clausii* (BC), *Bifidobacterium infantis* (BI), *Bifidobacterium lactis* (BL), *Lactobacillus acidophilus* (LA), *Lactobacillus bularicus* (LB), *Lactococcus casei* (LC), *Lactobacillus delbrueckii subsp. bulgaris* (LD), *Lactobacillus GG* (LGG), *Lactococcus lactis* (LL),*Lactococcus plantarum* (LP),*Lactococcus rhamnosus* (LR), *Lactobacillus sporogens* (LS), Fructo-Oligosaccaride (FOS), *Saccharomyces boulardii* (SB), *Saccharomyces florentinus* (SF), *Streptococcus thermophilus* (ST), Not available (NA)
OUTCOMES: Incidence of diarrhea (ID), Mean duration of diarhea (MDD), Mean stool consistency (MSC), Mean stool frequency (MSF)

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

Study	Reason for exclusion
Adam 1977	Pediatric level data could not be ascertained
Beausoleil 2007	Did not include children
Brunser 2006	Did not include probiotics as intervention
Can 2006	Did not include children
Chapoy 1985	Not randomized
Contreras 1983	Not randomized
Czerwionka 2006	Not randomized
Dajani 2013	Pediatric level data could not be ascertained
Daschner 1979	Not randomized
Duman 2005	Not a pediatric population
Erdeve 2005	Letter to the editor regarding pediatric AAD
Guandalini 1988	Article could not be found
Honeycutt 2007	Did not administer probiotics concurrently with antibiotics
Hosjak 2010	AAD patient population excluded (studying nosocomial infections only)
Hurduc 2009	AAD outcome could not be obtained
Imase 2008	Not a pediatric population
Kim 2008	Did not include children
Kleinkauf 1959	Not randomized
Koning 2008	Did not include children
Lei 2006	Not associated with antibiotic use
Lin 2009	Participants were not taking antibiotics concurrently with probiotics, or this data could not be ascertained
Lionetti 2006	Used a gastro-intestinal symptoms rating scale that, while inclusive of stool frequency and consistency, did not report data specific to those outcomes

(*Continued*)

McFarland 2005	Letter to the editor regarding pediatric AAD
Michail 2011	Participants were not taking antibiotics concurrently with probiotics, or this data could not be ascertained
Michielutti 1996	A study of acute diarrhea not associated with antibiotic use
Morrow 2010	Not a pediatric population
Nista 2004	Not a pediatric population
Pancheva 2009	Participants were not taking antibiotics concurrently with probiotics, or this data could not be ascertained
Parfenov 2005	Participants were not taking antibiotics concurrently with probiotics, or this data could not be ascertained
Park 2007	Not a pediatric population
Penna 2009	Participants were not taking antibiotics concurrently with probiotics, or this data could not be ascertained
Plewinska 2006	Not randomized
Saavedra 1994	Participants were not taking antibiotics concurrently with probiotics, or this data could not be ascertained
Savas-Erdeve 2009	Involved *Sacchromyces boulardii* for pediatric infectious diarrhea (i.e., amebiasis-associated diarrhea) not antibiotic associated diarrhea
Schrezenmeir 2004	Did not report outcomes particular to AAD
Seki 2003	Not randomized
Siitonen 1990	Not a pediatric population
Simakachorn 2011	Participants were not taking antibiotics concurrently with probiotics, or this data could not be ascertained
Srinivasan 2006	Did not report outcomes particular to AAD
Szajewka 2001	Did not evaluate antibiotic use
Thomas 2001	Not a pediatric population
Tolone 2012	Had a high dose of prebiotics (>5 grams)
Valsecchi 2014	No diarrhea outcome
Wanke 2012	Probiotics not administered concurrently with antibiotics
Weizman 2005	Not associated with antibiotic use

(*Continued*)

Wenus 2008	Did not include children
Witsell 1995	Not a pediatric population
Zhao 2014	AAD outcome could not be obtained
Zoppi 2001	Primary outcome not diarrhea. A study of how antibiotics effect the gut flora

DATA AND ANALYSES

Comparison 1. Probiotics versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of diarrhea: Complete case	22	3898	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.35, 0.61]
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	15	1575	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.29, 0.61]
1.3 Incidence of Diarrhea: No treatment control	5	1550	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.25, 0.60]
2 Incidence of diarrhea: Probiotic dose	22	3898	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.35, 0.61]
2.1 ≥5 billion CFU of probiotic/day	11	1931	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.27, 0.51]
2.2 <5 billion CFU of probiotic/day	11	1967	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.41, 0.92]
3 Incidence of diarrhea: Probiotic species	22	3898	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.35, 0.61]
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	4	1611	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.17, 0.96]
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 thermophillus, 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]

3.11 Lactobacillus rhamnosus GG, Bifidobacterium animalis subsp. Lactis Bv-12, L. acidophilus LA-5	1	70	Risk Ratio (M-H, Random, 95% CI)	0.05 [0.01, 0.35]
3.12 Lactobasillus casei, Lactobacillus acidophilus, Lactobasillus reuteri, Lactobasillus bulgaricus, Streptococcus, Bifidobacterium bifidum, Bifidobacterium infantis	1	50	Risk Ratio (M-H, Random, 95% CI)	0.23 [0.07, 0.71]
3.13 Lactobacillus reuteri DSM 17938	1	97	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.06, 15.22]
3.14 Lactobacillus acidophilus, Lactobacillus rhamnosus, Lactobacillus bulgaricus, Lactobacillus casei, Streptococcus thermophilus, Bifidobacterium infantis and Bifidobacterium breve	1	66	Risk Ratio (M-H, Random, 95% CI)	0.25 [0.06, 1.09]
3.15 L. casei DN-114 001	1	86	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.18, 2.84]
3.16 Clostridium Butyricum and Bifidobacterium	1	372	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.26, 0.83]
4 Incidence of diarrhea: Risk of bias	22	3898	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.35, 0.61]
4.1 Low Risk	10	1344	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.30, 0.60]
4.2 High Risk	12	2554	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.33, 0.77]
5 Incidence of diarrhea: Strictness of definition	18	3611	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.32, 0.61]
5.1 > or = to Moderate	13	2845	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.29, 0.65]
5.2 < Moderate	5	766	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.22, 0.82]
6 Incidence of diarrhea: Definition of diarrhea	18	3891	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.26, 0.54]
6.1 3 or more watery/liquid stools for more than 2 days	1	70	Risk Ratio (M-H, Random, 95% CI)	0.08 [0.00, 1.39]
6.2 3 or more loose/watery/liquid stools per day for at least 2 consecutive days	12	1833	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.26, 0.51]
6.3 ≥3 watery/liquid stools per 24 hours	2	1082	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.15, 2.85]
6.4 ≥2 liquid stools per day on at least 2 occasions during study	2	258	Risk Ratio (M-H, Random, 95% CI)	0.24 [0.09, 0.65]
6.5 >=2 loose/watery/liquid stools for more than 2 days	1	70	Risk Ratio (M-H, Random, 95% CI)	0.05 [0.01, 0.35]
6.6 ≥2 liquid stools per 24 hr	1	98	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.29, 0.77]
6.7 ≥1 abnormally loose bowel movement per 24 hrs	1	38	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.61, 1.50]
6.8 2 or more BM over the patient's normal	1	372	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.26, 0.83]

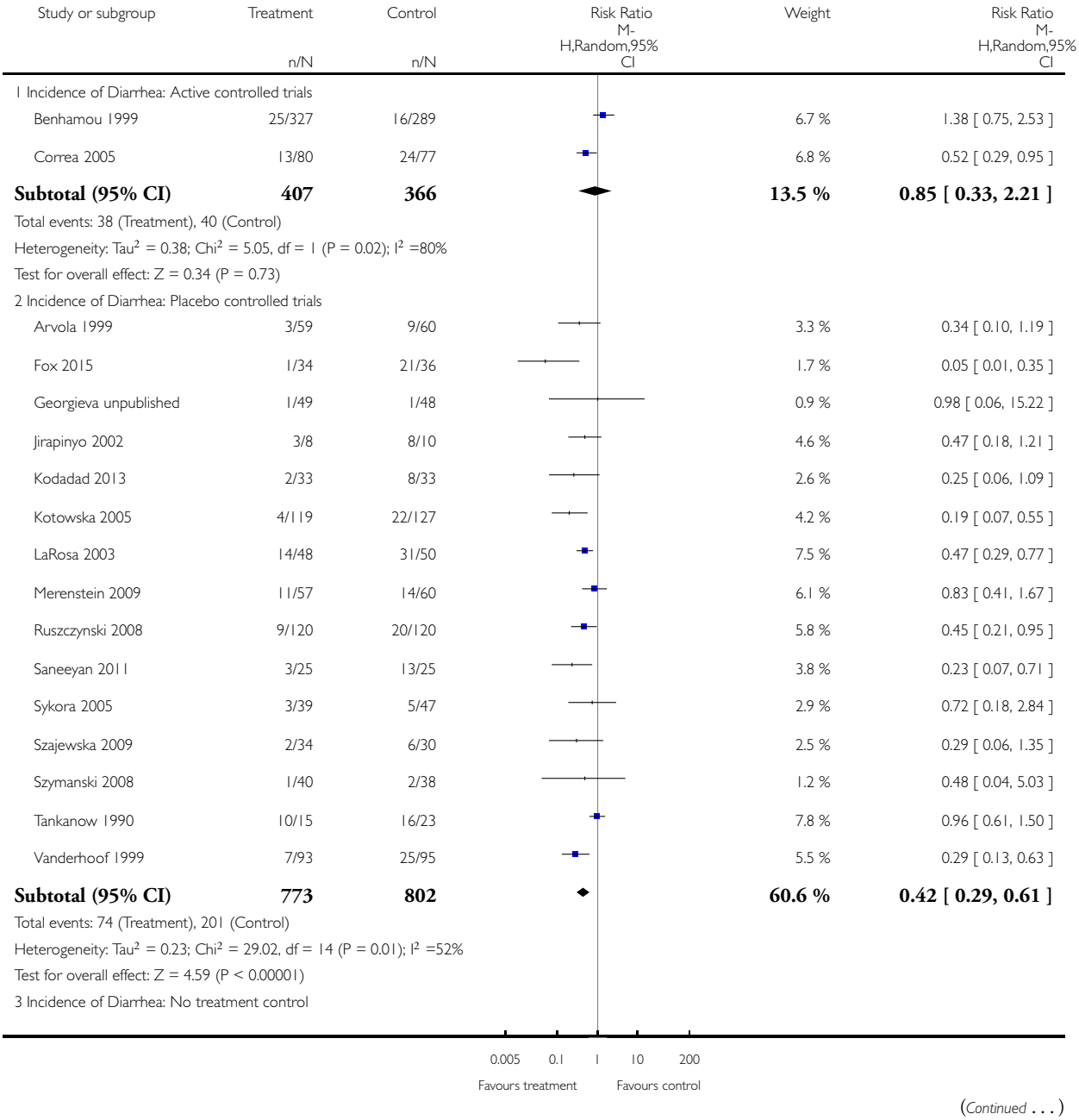
6.9 "Any of Above (Fox)"	1	70	Risk Ratio (M-H, Random, 95% CI)	0.04 [0.01, 0.27]
7 Incidence of diarrhea: Sensitivity analysis (complete case - fixed effects)	22	3898	Risk Ratio (M-H, Fixed, 95% CI)	0.44 [0.37, 0.53]
7.1 Active controlled	2	773	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.58, 1.32]
7.2 Placebo controlled	15	1575	Risk Ratio (M-H, Fixed, 95% CI)	0.40 [0.32, 0.50]
7.3 No treatment control	5	1550	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.27, 0.51]
8 Incidence of diarrhea: Sensitivity analysis (extreme-plausible analysis)	22	4529	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.54, 0.89]
8.1 Active controlled	2	948	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.40, 2.86]
8.2 Placebo controlled	15	1786	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.45, 0.85]
8.3 No treatment control	5	1795	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.49, 1.05]
9 Incidence of diarrhea: Probiotic dose (extreme-plausible analysis)	21	4511	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.55, 0.90]
9.1 ≥5 billion CFU of probiotic/day	10	2267	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.49, 0.90]
9.2 <5 billion CFU of probiotic/day	11	2244	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.50, 1.16]
10 Incidence of diarrhea: Diagnosis	18	2553	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.31, 0.56]
10.1 H. pylori	4	266	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.17, 0.63]
10.2 Respiratory Infections	5	952	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.31, 0.68]
10.3 Mixed	9	1335	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.23, 0.71]
11 Incidence of diarrhea: Industry sponsorship	12	1517	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.33, 0.76]
11.1 Industry Sponsored	7	1149	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.40, 0.86]
11.2 Non-Industry	5	368	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.11, 0.96]
12 Incidence of diarrhea: Inpatient versus outpatient	13	2176	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.34, 0.77]
12.1 Inpatient	5	834	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.26, 0.55]
12.2 Outpatient	8	1342	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.34, 1.02]
13 Incidence of diarrhea: Single strain versus multi strain	22	3898	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.35, 0.61]
13.1 Single Strain	11	2586	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.28, 0.62]
13.2 Multi Strain	11	1312	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.35, 0.77]
14 Adverse events: Complete case	16	2455	Risk Difference (M-H, Random, 95% CI)	0.00 [-0.01, 0.01]
15 Adverse events: Same event rate assumptions analysis	21	4369	Risk Difference (M-H, Random, 95% CI)	0.00 [-0.00, 0.01]
16 Adverse events: Risk of bias	16	2455	Risk Difference (M-H, Random, 95% CI)	0.00 [-0.01, 0.01]
16.1 Low RoB	9	1249	Risk Difference (M-H, Random, 95% CI)	0.00 [-0.01, 0.02]
16.2 High/Unclear	7	1206	Risk Difference (M-H, Random, 95% CI)	-.00 [-0.01, 0.01]
17 Mean duration of diarrhea: Complete case	5	897	Mean Difference (IV, Random, 95% CI)	-0.60 [-1.18, -0.02]
18 Mean stool frequency: Complete case	4	425	Mean Difference (IV, Random, 95% CI)	-0.30 [-0.60, -.00]

Analysis 1.1. Comparison 1 Probiotics versus control, Outcome 1 Incidence of diarrhea: Complete case.

Review: Probiotics for the prevention of pediatric antibiotic-associated diarrhea

Comparison: 1 Probiotics versus control

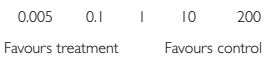
Outcome: 1 Incidence of diarrhea: Complete case



(*Continued . . .*)

(. . . *Continued*)

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Conway 2007	8/74	2/32		2.6 %	1.73 [0.39, 7.70]
Destura unpublished	3/162	7/161		3.0 %	0.43 [0.11, 1.62]
Erdeve 2004	14/244	42/222		6.9 %	0.30 [0.17, 0.54]
Shan 2013	11/139	42/144		6.6 %	0.27 [0.15, 0.51]
Zheng 2012	15/193	30/179		6.8 %	0.46 [0.26, 0.83]
Subtotal (95% CI)	**812**	**738**		**26.0 %**	**0.39 [0.25, 0.60]**
Total events: 51 (Treatment), 123 (Control)					
Heterogeneity: Tau^2 = 0.08; Chi^2 = 6.13, df = 4 (P = 0.19); I^2 =35%					
Test for overall effect: Z = 4.31 (P = 0.000016)					
Total (95% CI)	**1992**	**1906**		**100.0 %**	**0.46 [0.35, 0.61]**
Total events: 163 (Treatment), 364 (Control)					
Heterogeneity: Tau^2 = 0.21; Chi^2 = 47.01, df = 21 (P = 0.00094); I^2 =55%					
Test for overall effect: Z = 5.41 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 2.15, df = 2 (P = 0.34), I^2 =7%					

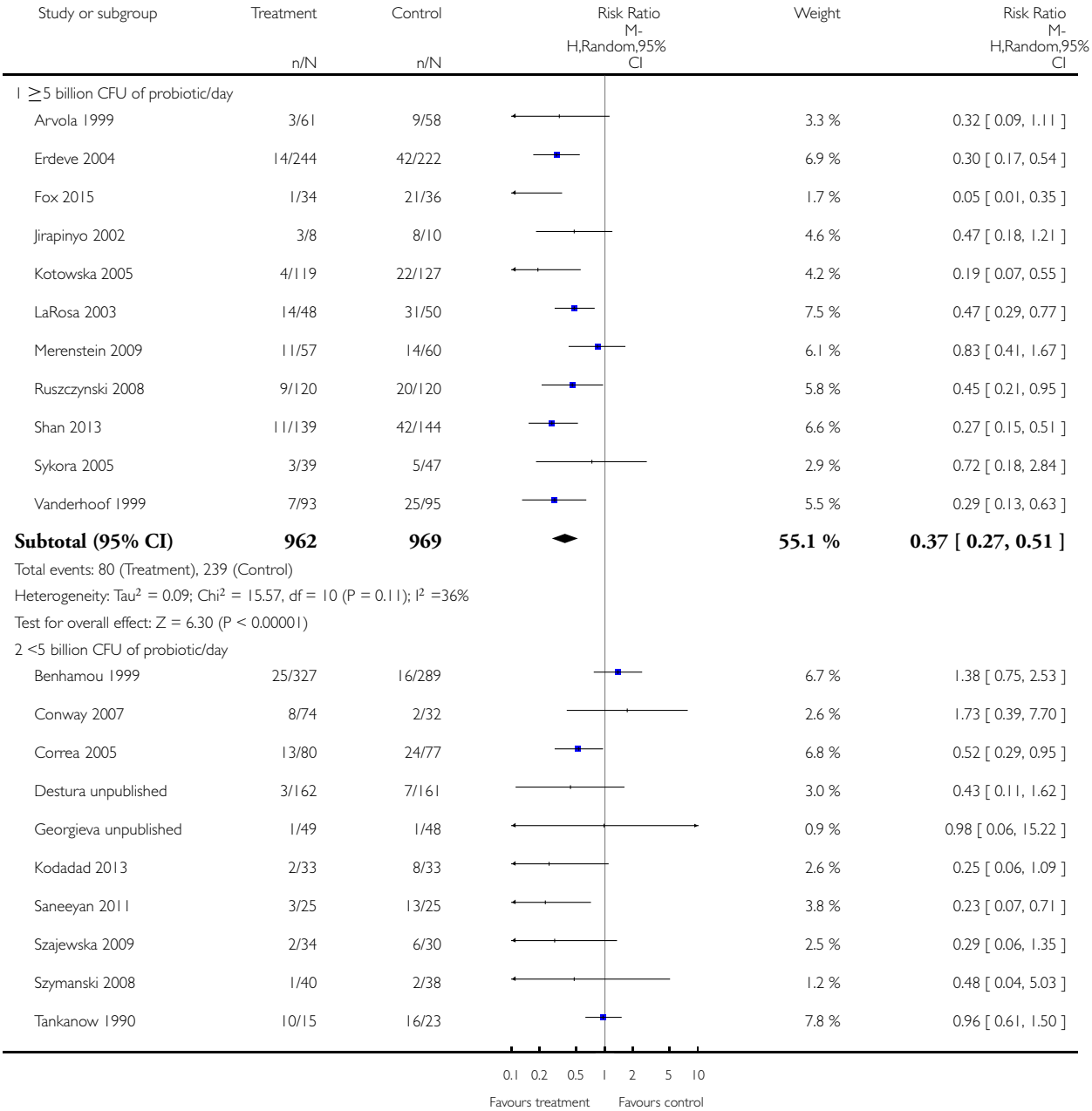


Analysis 1.2. Comparison 1 Probiotics versus control, Outcome 2 Incidence of diarrhea: Probiotic dose.

Review: Probiotics for the prevention of pediatric antibiotic-associated diarrhea

Comparison: 1 Probiotics versus control

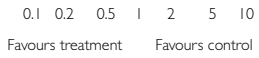
Outcome: 2 Incidence of diarrhea: Probiotic dose



(*Continued . . .*)

(. . . *Continued*)

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Zheng 2012	15/193	30/179		6.8 %	0.46 [0.26, 0.83]
Subtotal (95% CI)	**1032**	**935**		**44.9 %**	**0.62 [0.41, 0.92]**
Total events: 83 (Treatment), 125 (Control)					
Heterogeneity: Tau^2 = 0.17; Chi^2 = 18.93, df = 10 (P = 0.04); I^2 =47%					
Test for overall effect: Z = 2.39 (P = 0.017)					
Total (95% CI)	**1994**	**1904**		**100.0 %**	**0.46 [0.35, 0.61]**
Total events: 163 (Treatment), 364 (Control)					
Heterogeneity: Tau^2 = 0.21; Chi^2 = 47.16, df = 21 (P = 0.00089); I^2 =55%					
Test for overall effect: Z = 5.42 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 3.81, df = 1 (P = 0.05), I^2 =74%					



Analysis 1.3. Comparison 1 Probiotics versus control, Outcome 3 Incidence of diarrhea: Probiotic species.

Review: Probiotics for the prevention of pediatric antibiotic-associated diarrhea

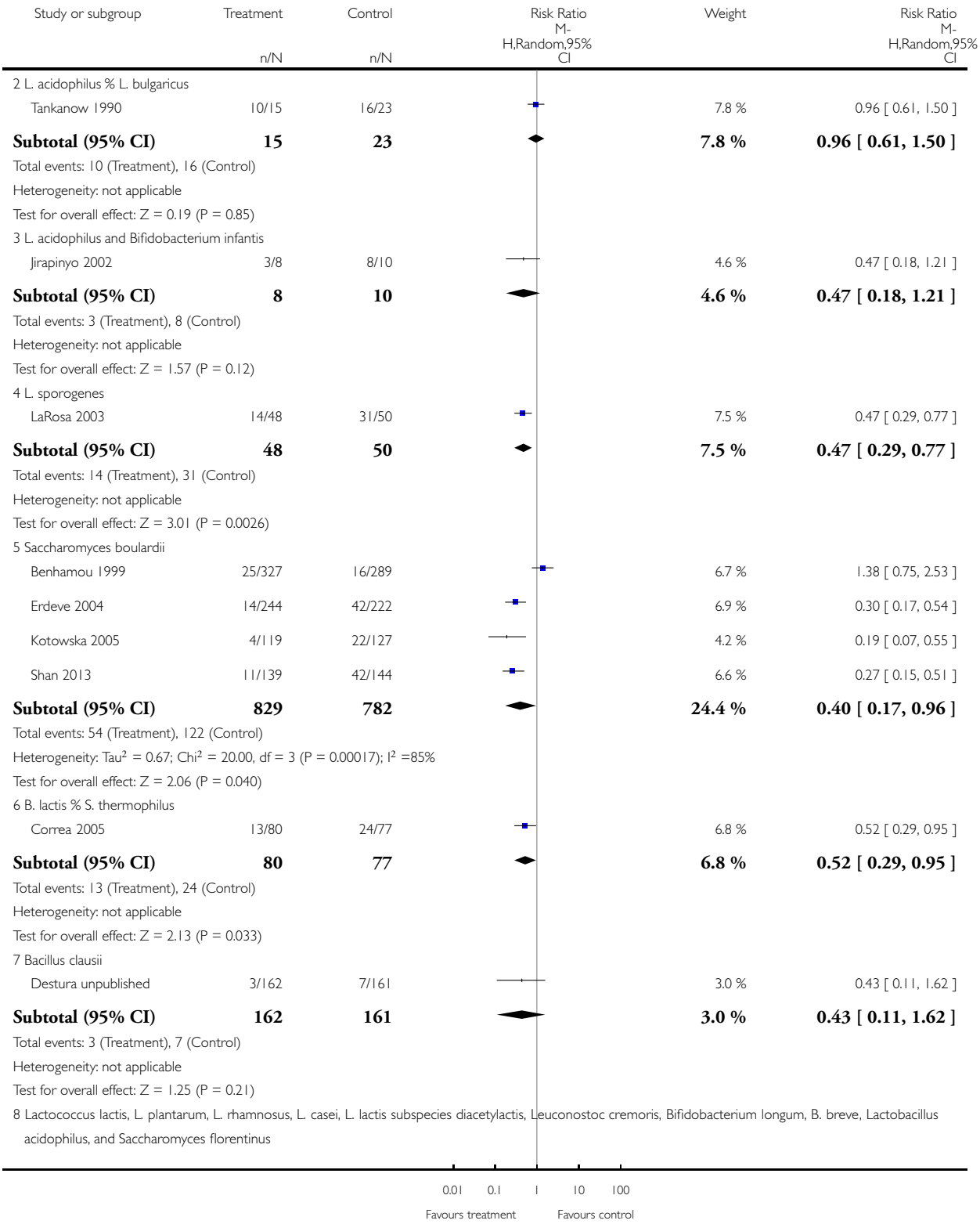
Comparison: 1 Probiotics versus control

Outcome: 3 Incidence of diarrhea: Probiotic species

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Lactobacillus rhamnosus (strains: GG and E/N, Oxy, Pen)					
Arvola 1999	3/60	9/59		3.3 %	0.33 [0.09, 1.15]
Ruszczynski 2008	9/120	20/120		5.8 %	0.45 [0.21, 0.95]
Szajewska 2009	2/34	6/30		2.5 %	0.29 [0.06, 1.35]
Vanderhoof 1999	7/93	25/95		5.5 %	0.29 [0.13, 0.63]
Subtotal (95% CI)	**307**	**304**		**17.1 %**	**0.35 [0.22, 0.56]**
Total events: 21 (Treatment), 60 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.75, df = 3 (P = 0.86); I^2 =0.0%					
Test for overall effect: Z = 4.34 (P = 0.000014)					

(*Continued* . . .)

(. . . *Continued*)



(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Merenstein 2009	11/57	14/60		6.1 %	0.83 [0.41, 1.67]
Subtotal (95% CI)	**57**	**60**		**6.1 %**	**0.83 [0.41, 1.67]**
Total events: 11 (Treatment), 14 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.53 (P = 0.60)					
9 Bifidobacterium longum PL03, Lactobacillus rhamnosus KL53A, and Lactobacillus plantarum PL02					
Szymanski 2008	1/40	2/38		1.2 %	0.48 [0.04, 5.03]
Subtotal (95% CI)	**40**	**38**		**1.2 %**	**0.48 [0.04, 5.03]**
Total events: 1 (Treatment), 2 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.62 (P = 0.54)					
10 Streptococcus thermophillus, L. acidophilus, B. anamalis subsp. lactus, L. delbrueckii subsp. bulgaris					
Conway 2007	8/74	2/32		2.6 %	1.73 [0.39, 7.70]
Subtotal (95% CI)	**74**	**32**		**2.6 %**	**1.73 [0.39, 7.70]**
Total events: 8 (Treatment), 2 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.72 (P = 0.47)					
11 Lactobacillus rhamnosus GG, Bifidobacterium animalis subsp. Lactis Bv-12, L. acidophilus LA-5					
Fox 2015	1/34	21/36		1.7 %	0.05 [0.01, 0.35]
Subtotal (95% CI)	**34**	**36**		**1.7 %**	**0.05 [0.01, 0.35]**
Total events: 1 (Treatment), 21 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.00 (P = 0.0027)					
12 Lactobasillus casei, Lactobacillus acidophilus, Lactobasillus reuteri, Lactobasillus bulgaricus, Streptococcus, Bifidobacterium bifidum, Bifidobacterium infantis					
Saneeyan 2011	3/25	13/25		3.8 %	0.23 [0.07, 0.71]
Subtotal (95% CI)	**25**	**25**		**3.8 %**	**0.23 [0.07, 0.71]**
Total events: 3 (Treatment), 13 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.55 (P = 0.011)					
13 Lactobacillus reuteri DSM 17938					
Georgieva unpublished	1/49	1/48		0.9 %	0.98 [0.06, 15.22]
Subtotal (95% CI)	**49**	**48**		**0.9 %**	**0.98 [0.06, 15.22]**
Total events: 1 (Treatment), 1 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.01 (P = 0.99)					
14 Lactobacillus acidophilus, Lactobacillus rhamnosus, Lactobacillus bulgaricus, Lactobacillus casei, Streptococcus thermophilus, Bifidobacterium infantis and Bifidobacterium breve					
Kodadad 2013	2/33	8/33		2.6 %	0.25 [0.06, 1.09]
Subtotal (95% CI)	**33**	**33**		**2.6 %**	**0.25 [0.06, 1.09]**

(*Continued* . . .)

(. . . *Continued*)

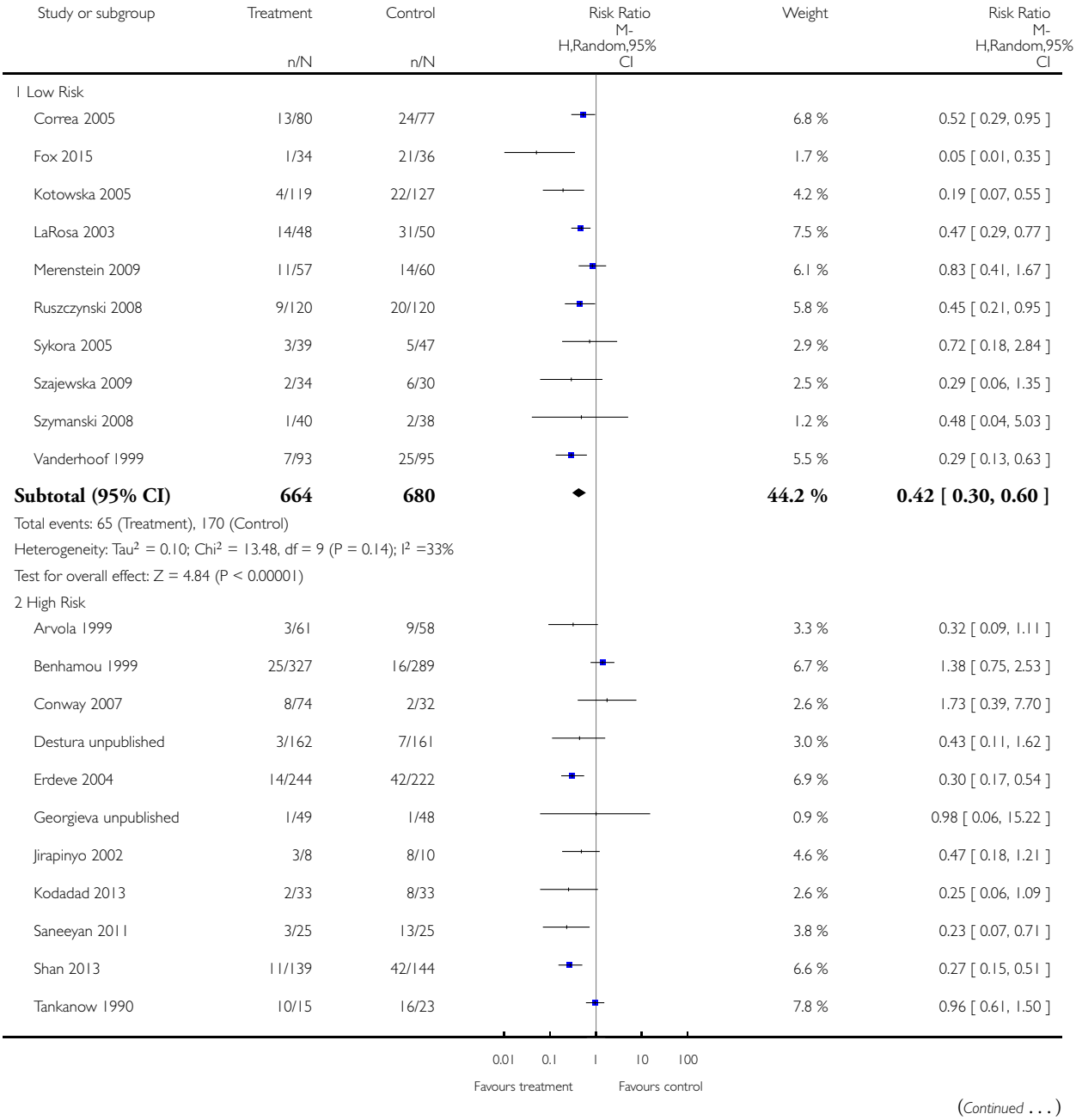
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Total events: 2 (Treatment), 8 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.85 (P = 0.065)					
15 L. casei DN-114 001					
Sykora 2005	3/39	5/47		2.9 %	0.72 [0.18, 2.84]
Subtotal (95% CI)	**39**	**47**		**2.9 %**	**0.72 [0.18, 2.84]**
Total events: 3 (Treatment), 5 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.46 (P = 0.64)					
16 Clostridium Butyricum and Bifidobacterium					
Zheng 2012	15/193	30/179		6.8 %	0.46 [0.26, 0.83]
Subtotal (95% CI)	**193**	**179**		**6.8 %**	**0.46 [0.26, 0.83]**
Total events: 15 (Treatment), 30 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.57 (P = 0.010)					
Total (95% CI)	**1993**	**1905**		**100.0 %**	**0.46 [0.35, 0.61]**
Total events: 163 (Treatment), 364 (Control)					
Heterogeneity: Tau^2 = 0.21; Chi^2 = 47.08, df = 21 (P = 0.00092); I^2 =55%					
Test for overall effect: Z = 5.42 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 23.64, df = 15 (P = 0.07), I^2 =37%					

Analysis 1.4. Comparison 1 Probiotics versus control, Outcome 4 Incidence of diarrhea: Risk of bias.

Review: Probiotics for the prevention of pediatric antibiotic-associated diarrhea

Comparison: 1 Probiotics versus control

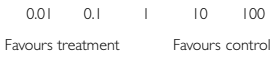
Outcome: 4 Incidence of diarrhea: Risk of bias



(*Continued . . .*)

(. . . *Continued*)

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Zheng 2012	15/193	30/179		6.8 %	0.46 [0.26, 0.83]
Subtotal (95% CI)	**1330**	**1224**		**55.8 %**	**0.50 [0.33, 0.77]**
Total events: 98 (Treatment), 194 (Control)					
Heterogeneity: Tau^2 = 0.31; Chi^2 = 32.07, df = 11 (P = 0.00074); I^2 =66%					
Test for overall effect: Z = 3.18 (P = 0.0015)					
Total (95% CI)	**1994**	**1904**		**100.0 %**	**0.46 [0.35, 0.61]**
Total events: 163 (Treatment), 364 (Control)					
Heterogeneity: Tau^2 = 0.21; Chi^2 = 47.16, df = 21 (P = 0.00089); I^2 =55%					
Test for overall effect: Z = 5.42 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 0.38, df = 1 (P = 0.54), I^2 =0.0%					

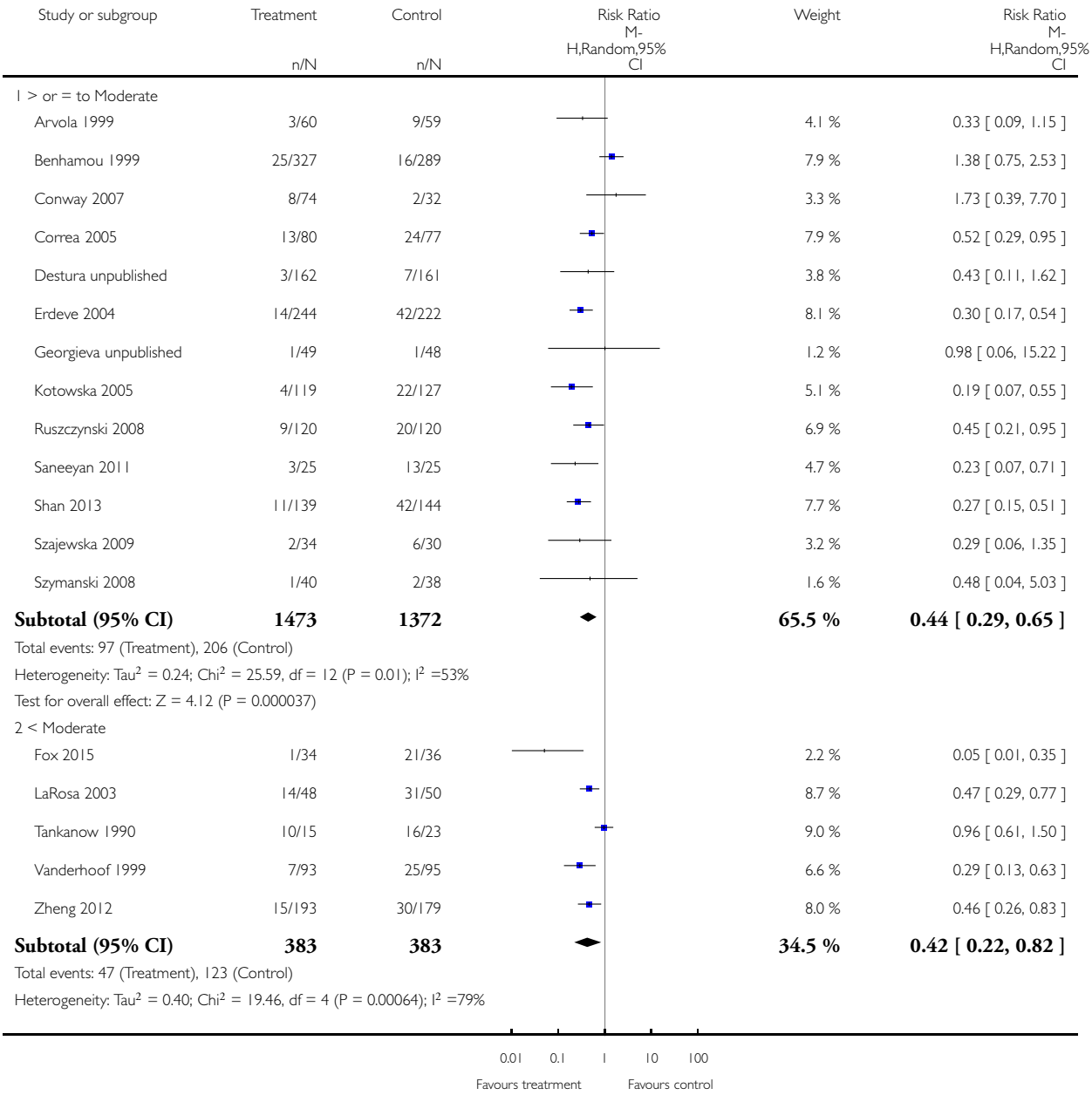


Analysis 1.5. Comparison 1 Probiotics versus control, Outcome 5 Incidence of diarrhea: Strictness of definition.

Review: Probiotics for the prevention of pediatric antibiotic-associated diarrhea

Comparison: 1 Probiotics versus control

Outcome: 5 Incidence of diarrhea: Strictness of definition



(*Continued . . .*)

(. . . *Continued*)

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Test for overall effect: Z = 2.57 (P = 0.010)					
Total (95% CI)	**1856**	**1755**	◆	**100.0 %**	**0.44 [0.32, 0.61]**
Total events: 144 (Treatment), 329 (Control)					
Heterogeneity: Tau^2 = 0.25; Chi^2 = 43.98, df = 17 (P = 0.00034); I^2 =61%					
Test for overall effect: Z = 4.98 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 0.01, df = 1 (P = 0.94), I^2 =0.0%					

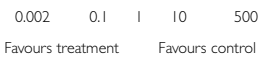
Analysis 1.6. Comparison 1 Probiotics versus control, Outcome 6 Incidence of diarrhea: Definition of diarrhea.

Review: Probiotics for the prevention of pediatric antibiotic-associated diarrhea

Comparison: 1 Probiotics versus control

Outcome: 6 Incidence of diarrhea: Definition of diarrhea

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 3 or more watery/liquid stools for more than 2 days					
Fox 2015	0/34	6/36	←	1.3 %	0.08 [0.00, 1.39]
Subtotal (95% CI)	**34**	**36**	◆	**1.3 %**	**0.08 [0.00, 1.39]**
Total events: 0 (Treatment), 6 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.73 (P = 0.083)					
2 3 or more loose/watery/liquid stools per day for at least 2 consecutive days					
Arvola 1999	3/60	9/59		4.2 %	0.33 [0.09, 1.15]
Conway 2007	8/74	2/32		3.4 %	1.73 [0.39, 7.70]
Correa 2005	13/80	24/77		7.1 %	0.52 [0.29, 0.95]
Destura unpublished	3/162	7/161		3.9 %	0.43 [0.11, 1.62]
Fox 2015	0/34	16/36	←	1.4 %	0.03 [0.00, 0.51]



(*Continued* . . .)

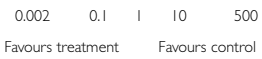
(. . . *Continued*)

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Georgieva unpublished	1/49	1/48		1.4 %	0.98 [0.06, 15.22]
Kotowska 2005	4/119	22/127		5.0 %	0.19 [0.07, 0.55]
Ruszczynski 2008	9/120	20/120		6.4 %	0.45 [0.21, 0.95]
Saneeyan 2011	3/25	13/25		4.7 %	0.23 [0.07, 0.71]
Shan 2013	11/139	42/144		7.0 %	0.27 [0.15, 0.51]
Szajewska 2009	2/34	6/30		3.4 %	0.29 [0.06, 1.35]
Szymanski 2008	1/40	2/38		1.8 %	0.48 [0.04, 5.03]
Subtotal (95% CI)	**936**	**897**		**49.7 %**	**0.37 [0.26, 0.51]**
Total events: 58 (Treatment), 164 (Control)					
Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 12.83$, df = 11 (P = 0.30); $I^2 = 14\%$					
Test for overall effect: Z = 5.80 (P < 0.00001)					
3 ≥3 watery/liquid stools per 24 hours					
Benhamou 1999	25/327	16/289		7.0 %	1.38 [0.75, 2.53]
Erdeve 2004	14/244	42/222		7.2 %	0.30 [0.17, 0.54]
Subtotal (95% CI)	**571**	**511**		**14.2 %**	**0.65 [0.15, 2.85]**
Total events: 39 (Treatment), 58 (Control)					
Heterogeneity: $Tau^2 = 1.06$; $Chi^2 = 12.60$, df = 1 (P = 0.00038); $I^2 = 92\%$					
Test for overall effect: Z = 0.58 (P = 0.56)					
4 ≥2 liquid stools per day on at least 2 occasions during study					
Fox 2015	0/34	8/36		1.3 %	0.06 [0.00, 1.04]
Vanderhoof 1999	7/93	25/95		6.2 %	0.29 [0.13, 0.63]
Subtotal (95% CI)	**127**	**131**		**7.5 %**	**0.24 [0.09, 0.65]**
Total events: 7 (Treatment), 33 (Control)					
Heterogeneity: $Tau^2 = 0.14$; $Chi^2 = 1.12$, df = 1 (P = 0.29); $I^2 = 11\%$					
Test for overall effect: Z = 2.79 (P = 0.0052)					
5 >=2 loose/watery/liquid stools for more than 2 days					
Fox 2015	1/34	21/36		2.4 %	0.05 [0.01, 0.35]
Subtotal (95% CI)	**34**	**36**		**2.4 %**	**0.05 [0.01, 0.35]**
Total events: 1 (Treatment), 21 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.00 (P = 0.0027)					
6 ≥2 liquid stools per 24 hr					
LaRosa 2003	14/48	31/50		7.6 %	0.47 [0.29, 0.77]
Subtotal (95% CI)	**48**	**50**		**7.6 %**	**0.47 [0.29, 0.77]**
Total events: 14 (Treatment), 31 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.01 (P = 0.0026)					
7 ≥1 abnormally loose bowel movement per 24 hrs					

(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Tankanow 1990	10/15	16/23		7.8 %	0.96 [0.61, 1.50]
Subtotal (95% CI)	**15**	**23**		**7.8 %**	**0.96 [0.61, 1.50]**
Total events: 10 (Treatment), 16 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.19 (P = 0.85)					
8 2 or more BM over the patient's normal					
Zheng 2012	15/193	30/179		7.1 %	0.46 [0.26, 0.83]
Subtotal (95% CI)	**193**	**179**		**7.1 %**	**0.46 [0.26, 0.83]**
Total events: 15 (Treatment), 30 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.57 (P = 0.010)					
9 "Any of Above (Fox)"					
Fox 2015	1/34	27/36		2.4 %	0.04 [0.01, 0.27]
Subtotal (95% CI)	**34**	**36**		**2.4 %**	**0.04 [0.01, 0.27]**
Total events: 1 (Treatment), 27 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.27 (P = 0.0011)					
Total (95% CI)	**1992**	**1899**		**100.0 %**	**0.38 [0.26, 0.54]**
Total events: 145 (Treatment), 386 (Control)					
Heterogeneity: Tau^2 = 0.37; Chi^2 = 61.78, df = 21 (P<0.00001); I^2 =66%					
Test for overall effect: Z = 5.41 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 26.40, df = 8 (P = 0.00), I^2 =70%					

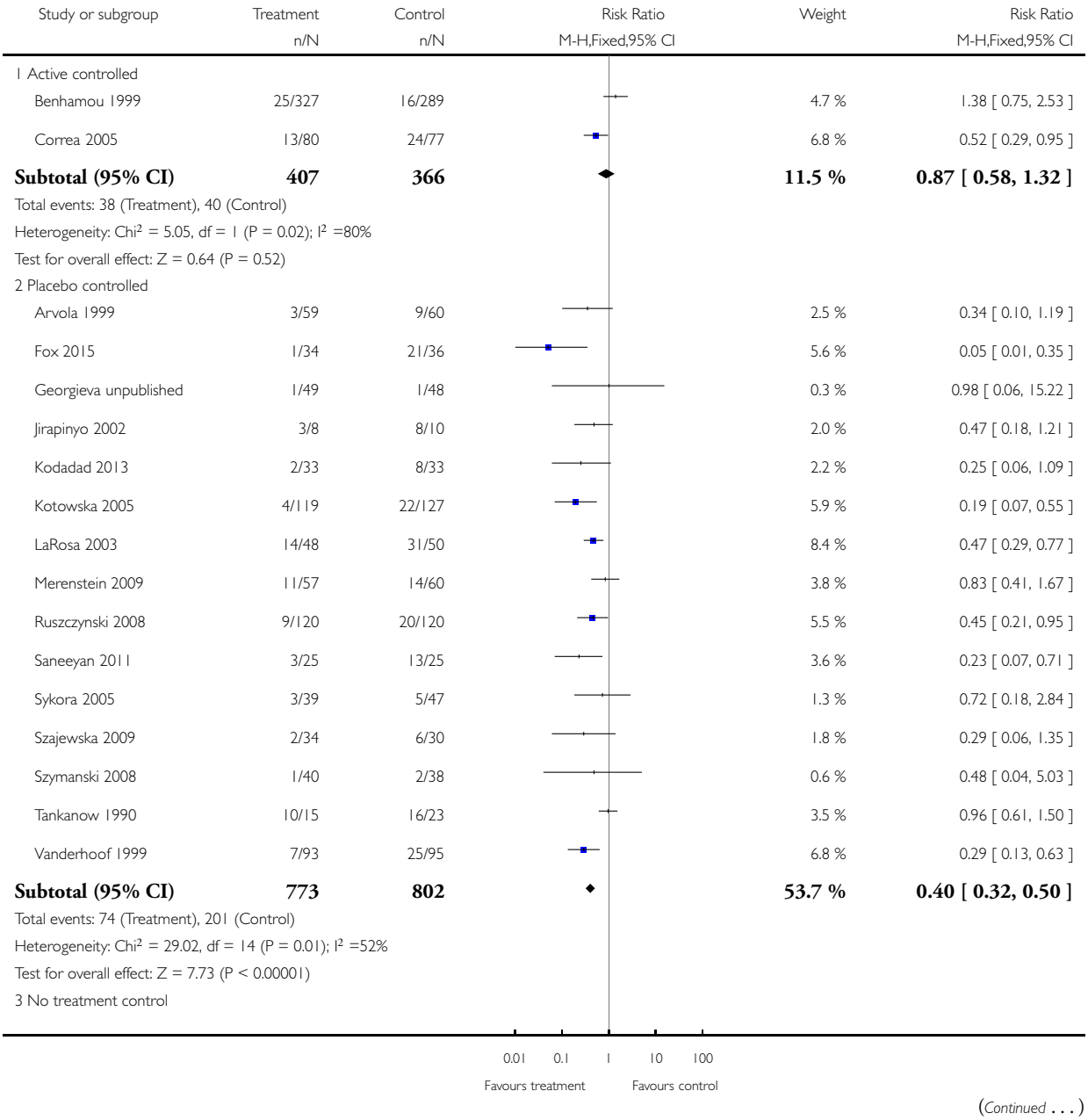


Analysis 1.7. Comparison 1 Probiotics versus control, Outcome 7 Incidence of diarrhea: Sensitivity analysis (complete case - fixed effects).

Review: Probiotics for the prevention of pediatric antibiotic-associated diarrhea

Comparison: 1 Probiotics versus control

Outcome: 7 Incidence of diarrhea: Sensitivity analysis (complete case - fixed effects)



(*Continued . . .*)

(. . . *Continued*)

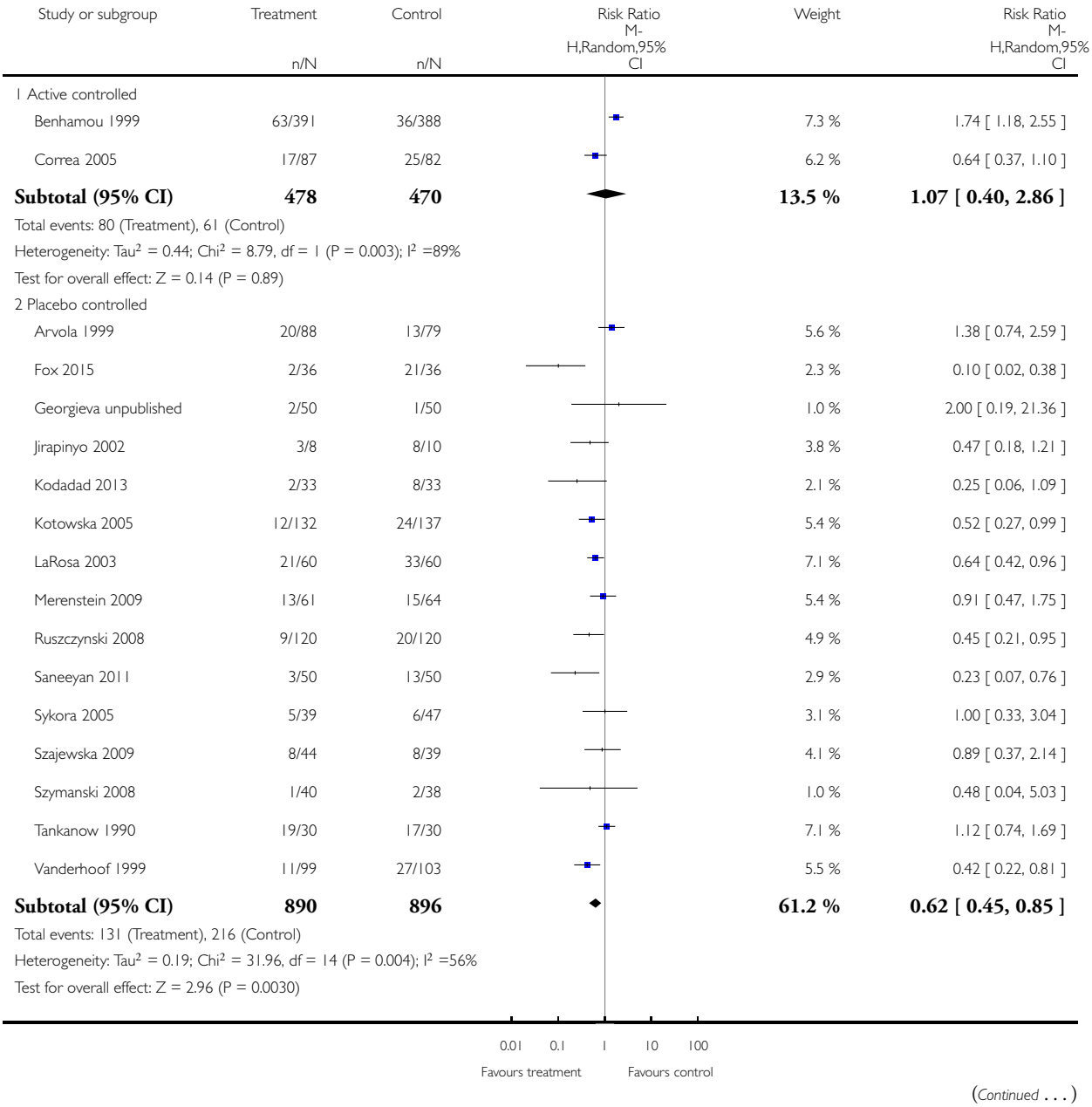
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Conway 2007	8/74	2/32		0.8 %	1.73 [0.39, 7.70]
Destura unpublished	3/162	7/161		1.9 %	0.43 [0.11, 1.62]
Erdeve 2004	14/244	42/222		12.2 %	0.30 [0.17, 0.54]
Shan 2013	11/139	42/144		11.4 %	0.27 [0.15, 0.51]
Zheng 2012	15/193	30/179		8.6 %	0.46 [0.26, 0.83]
Subtotal (95% CI)	**812**	**738**		**34.9 %**	**0.37 [0.27, 0.51]**
Total events: 51 (Treatment), 123 (Control)					
Heterogeneity: Chi^2 = 6.13, df = 4 (P = 0.19); I^2 =35%					
Test for overall effect: Z = 6.12 (P < 0.00001)					
Total (95% CI)	**1992**	**1906**		**100.0 %**	**0.44 [0.37, 0.53]**
Total events: 163 (Treatment), 364 (Control)					
Heterogeneity: Chi^2 = 47.01, df = 21 (P = 0.00094); I^2 =55%					
Test for overall effect: Z = 9.40 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 12.27, df = 2 (P = 0.00), I^2 =84%					

Analysis 1.8. Comparison 1 Probiotics versus control, Outcome 8 Incidence of diarrhea: Sensitivity analysis (extreme-plausible analysis).

Review: Probiotics for the prevention of pediatric antibiotic-associated diarrhea

Comparison: 1 Probiotics versus control

Outcome: 8 Incidence of diarrhea: Sensitivity analysis (extreme-plausible analysis)



(*Continued* . . .)

(. . . *Continued*)

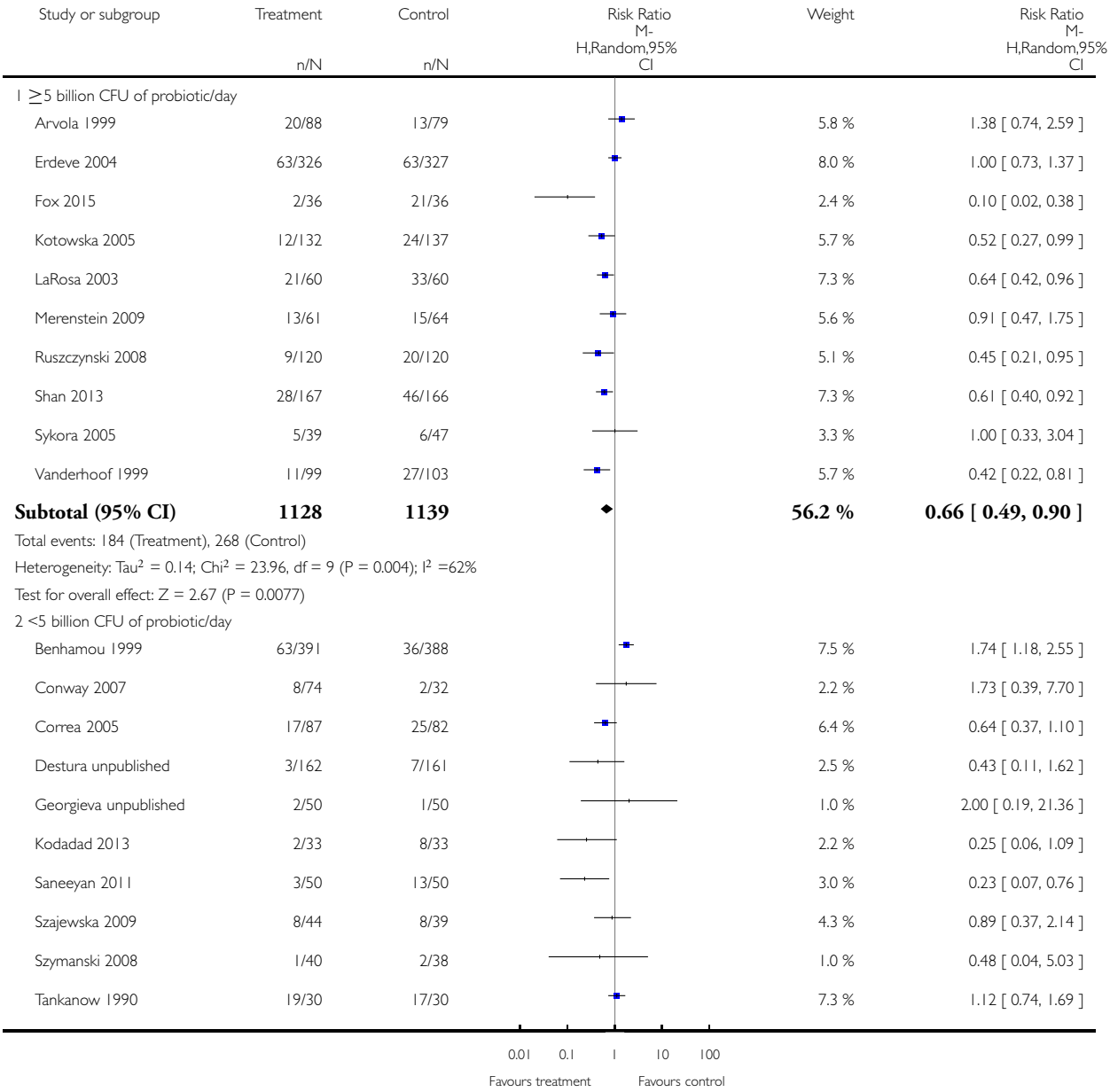
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
3 No treatment control					
Conway 2007	8/74	2/32		2.1 %	1.73 [0.39, 7.70]
Destura unpublished	3/162	7/161		2.4 %	0.43 [0.11, 1.62]
Erdeve 2004	63/326	63/327		7.7 %	1.00 [0.73, 1.37]
Shan 2013	28/167	46/166		7.0 %	0.61 [0.40, 0.92]
Zheng 2012	17/197	31/183		6.1 %	0.51 [0.29, 0.89]
Subtotal (95% CI)	**926**	**869**		**25.3 %**	**0.72 [0.49, 1.05]**
Total events: 119 (Treatment), 149 (Control)					
Heterogeneity: Tau^2 = 0.08; Chi^2 = 8.02, df = 4 (P = 0.09); I^2 =50%					
Test for overall effect: Z = 1.71 (P = 0.088)					
Total (95% CI)	**2294**	**2235**		**100.0 %**	**0.69 [0.54, 0.89]**
Total events: 330 (Treatment), 426 (Control)					
Heterogeneity: Tau^2 = 0.18; Chi^2 = 57.21, df = 21 (P = 0.00003); I^2 =63%					
Test for overall effect: Z = 2.93 (P = 0.0034)					
Test for subgroup differences: Chi^2 = 1.27, df = 2 (P = 0.53), I^2 =0.0%					

Analysis 1.9. Comparison 1 Probiotics versus control, Outcome 9 Incidence of diarrhea: Probiotic dose (extreme-plausible analysis).

Review: Probiotics for the prevention of pediatric antibiotic-associated diarrhea

Comparison: 1 Probiotics versus control

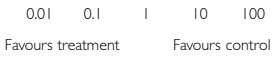
Outcome: 9 Incidence of diarrhea: Probiotic dose (extreme-plausible analysis)



(*Continued . . .*)

(. . . *Continued*)

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Zheng 2012	17/197	31/183		6.3 %	0.51 [0.29, 0.89]
Subtotal (95% CI)	**1158**	**1086**		**43.8 %**	**0.76 [0.50, 1.16]**
Total events: 143 (Treatment), 150 (Control)					
Heterogeneity: Tau^2 = 0.26; Chi^2 = 28.40, df = 10 (P = 0.002); I^2 =65%					
Test for overall effect: Z = 1.29 (P = 0.20)					
Total (95% CI)	**2286**	**2225**		**100.0 %**	**0.70 [0.55, 0.90]**
Total events: 327 (Treatment), 418 (Control)					
Heterogeneity: Tau^2 = 0.18; Chi^2 = 56.05, df = 20 (P = 0.00003); I^2 =64%					
Test for overall effect: Z = 2.74 (P = 0.0061)					
Test for subgroup differences: Chi^2 = 0.27, df = 1 (P = 0.61), I^2 =0.0%					



Analysis 1.10. Comparison 1 Probiotics versus control, Outcome 10 Incidence of diarrhea: Diagnosis.

Review: Probiotics for the prevention of pediatric antibiotic-associated diarrhea

Comparison: 1 Probiotics versus control

Outcome: 10 Incidence of diarrhea: Diagnosis

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 H. pylori					
Kodadad 2013	2/33	8/33		3.2 %	0.25 [0.06, 1.09]
Saneeyan 2011	3/25	13/25		4.7 %	0.23 [0.07, 0.71]
Sykora 2005	3/39	5/47		3.6 %	0.72 [0.18, 2.84]
Szajewska 2009	2/34	6/30		3.0 %	0.29 [0.06, 1.35]
Subtotal (95% CI)	**131**	**135**		**14.6 %**	**0.32 [0.17, 0.63]**
Total events: 10 (Treatment), 32 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 1.81, df = 3 (P = 0.61); I^2 =0.0%					
Test for overall effect: Z = 3.29 (P = 0.0010)					

(*Continued* . . .)

(. . . *Continued*)

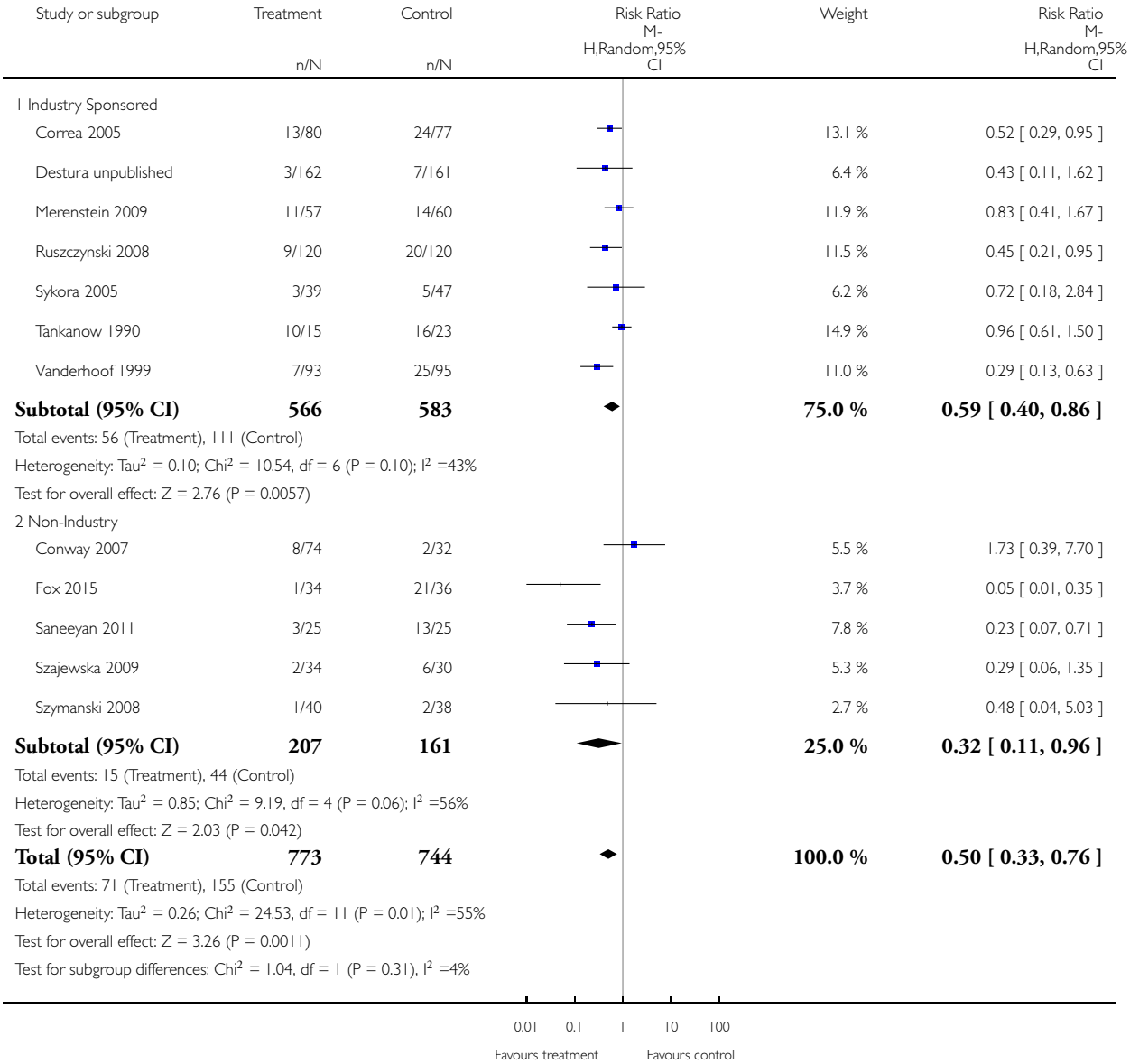
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
2 Respiratory Infections					
Arvola 1999	3/59	9/60		4.1 %	0.34 [0.10, 1.19]
Kotowska 2005	4/119	22/127		5.3 %	0.19 [0.07, 0.55]
LaRosa 2003	14/48	31/50		10.3 %	0.47 [0.29, 0.77]
Merenstein 2009	11/57	14/60		8.0 %	0.83 [0.41, 1.67]
Zheng 2012	15/193	30/179		9.2 %	0.46 [0.26, 0.83]
Subtotal (95% CI)	**476**	**476**		**36.9 %**	**0.46 [0.31, 0.68]**
Total events: 47 (Treatment), 106 (Control)					
Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 5.69$, df = 4 (P = 0.22); $I^2 = 30\%$					
Test for overall effect: Z = 3.90 (P = 0.000095)					
3 Mixed					
Destura unpublished	3/162	7/161		3.7 %	0.43 [0.11, 1.62]
Fox 2015	1/34	21/36		2.0 %	0.05 [0.01, 0.35]
Georgieva unpublished	1/49	1/48		1.1 %	0.98 [0.06, 15.22]
Jirapinyo 2002	3/8	8/10		5.9 %	0.47 [0.18, 1.21]
Ruszczynski 2008	9/120	20/120		7.6 %	0.45 [0.21, 0.95]
Shan 2013	11/139	42/144		8.8 %	0.27 [0.15, 0.51]
Szymanski 2008	1/40	2/38		1.5 %	0.48 [0.04, 5.03]
Tankanow 1990	10/15	16/23		10.8 %	0.96 [0.61, 1.50]
Vanderhoof 1999	7/93	25/95		7.2 %	0.29 [0.13, 0.63]
Subtotal (95% CI)	**660**	**675**		**48.6 %**	**0.40 [0.23, 0.71]**
Total events: 46 (Treatment), 142 (Control)					
Heterogeneity: $Tau^2 = 0.43$; $Chi^2 = 24.84$, df = 8 (P = 0.002); $I^2 = 68\%$					
Test for overall effect: Z = 3.13 (P = 0.0018)					
Total (95% CI)	**1267**	**1286**		**100.0 %**	**0.42 [0.31, 0.56]**
Total events: 103 (Treatment), 280 (Control)					
Heterogeneity: $Tau^2 = 0.16$; $Chi^2 = 31.76$, df = 17 (P = 0.02); $I^2 = 46\%$					
Test for overall effect: Z = 5.72 (P < 0.00001)					
Test for subgroup differences: $Chi^2 = 0.84$, df = 2 (P = 0.66), $I^2 = 0.0\%$					

Analysis 1.11. Comparison 1 Probiotics versus control, Outcome 11 Incidence of diarrhea: Industry sponsorship.

Review: Probiotics for the prevention of pediatric antibiotic-associated diarrhea

Comparison: 1 Probiotics versus control

Outcome: 11 Incidence of diarrhea: Industry sponsorship

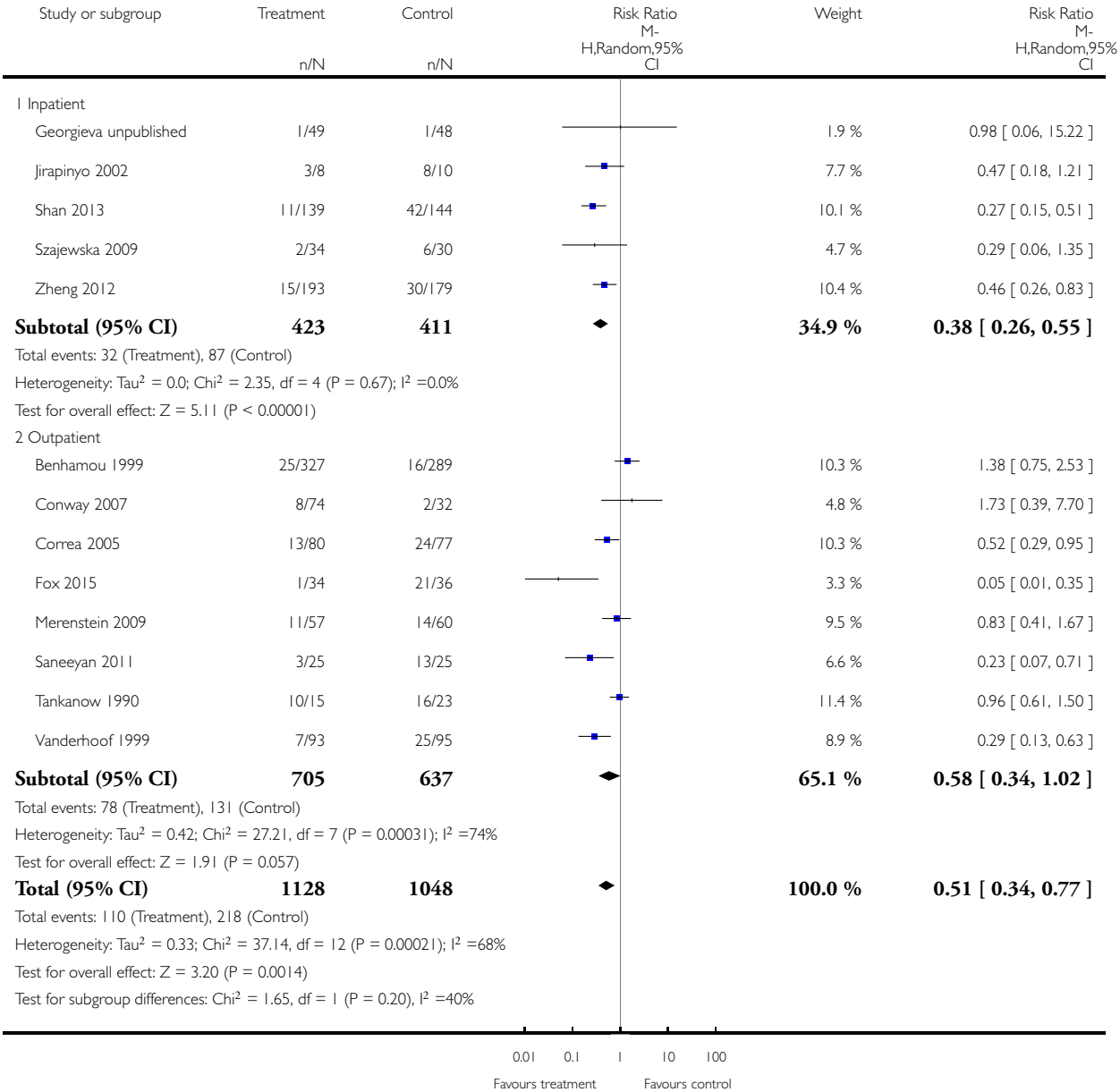


Analysis 1.12. Comparison 1 Probiotics versus control, Outcome 12 Incidence of diarrhea: Inpatient versus outpatient.

Review: Probiotics for the prevention of pediatric antibiotic-associated diarrhea

Comparison: 1 Probiotics versus control

Outcome: 12 Incidence of diarrhea: Inpatient versus outpatient



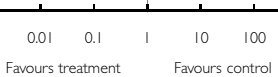
Analysis 1.13. Comparison 1 Probiotics versus control, Outcome 13 Incidence of diarrhea: Single strain versus multi strain.

Review: Probiotics for the prevention of pediatric antibiotic-associated diarrhea

Comparison: 1 Probiotics versus control

Outcome: 13 Incidence of diarrhea: Single strain versus multi strain

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Single Strain					
Arvola 1999	3/59	9/60		3.3 %	0.34 [0.10, 1.19]
Benhamou 1999	25/327	16/289		6.7 %	1.38 [0.75, 2.53]
Destura unpublished	3/162	7/161		3.0 %	0.43 [0.11, 1.62]
Erdeve 2004	14/244	42/222		6.9 %	0.30 [0.17, 0.54]
Georgieva unpublished	1/49	1/48		0.9 %	0.98 [0.06, 15.22]
Kotowska 2005	4/119	22/127		4.2 %	0.19 [0.07, 0.55]
LaRosa 2003	14/48	31/50		7.5 %	0.47 [0.29, 0.77]
Shan 2013	11/139	42/144		6.6 %	0.27 [0.15, 0.51]
Sykora 2005	3/39	5/47		2.9 %	0.72 [0.18, 2.84]
Szajewska 2009	2/34	6/30		2.5 %	0.29 [0.06, 1.35]
Vanderhoof 1999	7/93	25/95		5.5 %	0.29 [0.13, 0.63]
Subtotal (95% CI)	**1313**	**1273**		**50.2 %**	**0.41 [0.28, 0.62]**
Total events: 87 (Treatment), 206 (Control)					
Heterogeneity: $Tau^2 = 0.22$; $Chi^2 = 22.48$, df = 10 (P = 0.01); $I^2 = 56\%$					
Test for overall effect: Z = 4.31 (P = 0.000016)					
2 Multi Strain					
Conway 2007	8/74	2/32		2.6 %	1.73 [0.39, 7.70]
Correa 2005	13/80	24/77		6.8 %	0.52 [0.29, 0.95]
Fox 2015	1/34	21/36		1.7 %	0.05 [0.01, 0.35]
Jirapinyo 2002	3/8	8/10		4.6 %	0.47 [0.18, 1.21]
Kodadad 2013	2/33	8/33		2.6 %	0.25 [0.06, 1.09]
Merenstein 2009	11/57	14/60		6.1 %	0.83 [0.41, 1.67]
Ruszczynski 2008	9/120	20/120		5.8 %	0.45 [0.21, 0.95]
Saneeyan 2011	3/25	13/25		3.8 %	0.23 [0.07, 0.71]
Szymanski 2008	1/40	2/38		1.2 %	0.48 [0.04, 5.03]



(*Continued . . .*)

(. . . *Continued*)

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Tankanow 1990	10/15	16/23		7.8 %	0.96 [0.61, 1.50]
Zheng 2012	15/193	30/179		6.8 %	0.46 [0.26, 0.83]
Subtotal (95% CI)	**679**	**633**		**49.8 %**	**0.52 [0.35, 0.77]**
Total events: 76 (Treatment), 158 (Control)					
Heterogeneity: $Tau^2 = 0.21$; $Chi^2 = 21.81$, df = 10 (P = 0.02); I^2 =54%					
Test for overall effect: Z = 3.29 (P = 0.0010)					
Total (95% CI)	**1992**	**1906**		**100.0 %**	**0.46 [0.35, 0.61]**
Total events: 163 (Treatment), 364 (Control)					
Heterogeneity: $Tau^2 = 0.21$; $Chi^2 = 47.01$, df = 21 (P = 0.00094); I^2 =55%					
Test for overall effect: Z = 5.41 (P < 0.00001)					
Test for subgroup differences: $Chi^2 = 0.59$, df = 1 (P = 0.44), I^2 =0.0%					

Analysis 1.14. Comparison 1 Probiotics versus control, Outcome 14 Adverse events: Complete case.

Review: Probiotics for the prevention of pediatric antibiotic-associated diarrhea

Comparison: 1 Probiotics versus control

Outcome: 14 Adverse events: Complete case

Study or subgroup	Treatment n/N	Control n/N	Risk Difference M-H,Random,95% CI	Weight	Risk Difference M-H,Random,95% CI
Conway 2007	0/74	0/32		2.7 %	0.0 [-0.05, 0.05]
Correa 2005	5/80	0/77		1.8 %	0.06 [0.00, 0.12]
Destura unpublished	0/162	0/161		17.6 %	0.0 [-0.01, 0.01]
Fox 2015	3/34	11/36		0.2 %	-0.22 [-0.40, -0.04]
Jirapinyo 2002	0/8	0/10		0.2 %	0.0 [-0.19, 0.19]
Kodadad 2013	5/33	13/33		0.1 %	-0.24 [-0.45, -0.04]
Kotowska 2005	0/119	0/127		13.6 %	0.0 [-0.02, 0.02]
Merenstein 2009	1/57	1/60		2.6 %	0.00 [-0.05, 0.05]
Ruszczynski 2008	0/120	0/120		13.2 %	0.0 [-0.02, 0.02]
Shan 2013	0/139	0/144		15.7 %	0.0 [-0.01, 0.01]
Sykora 2005	4/39	4/47		0.4 %	0.02 [-0.11, 0.14]
Szajewska 2009	18/35	13/32		0.1 %	0.11 [-0.13, 0.35]
Szymanski 2008	0/40	0/38		2.4 %	0.0 [-0.05, 0.05]
Tankanow 1990	3/15	0/23		0.1 %	0.20 [-0.01, 0.41]
Vanderhoof 1999	0/93	0/95		9.8 %	0.0 [-0.02, 0.02]
Zheng 2012	0/193	0/179		19.5 %	0.0 [-0.01, 0.01]
Total (95% CI)	**1241**	**1214**		**100.0 %**	**0.00 [-0.01, 0.01]**

Total events: 39 (Treatment), 42 (Control)

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 20.71$, df = 15 (P = 0.15); $I^2 = 28\%$

Test for overall effect: Z = 0.20 (P = 0.84)

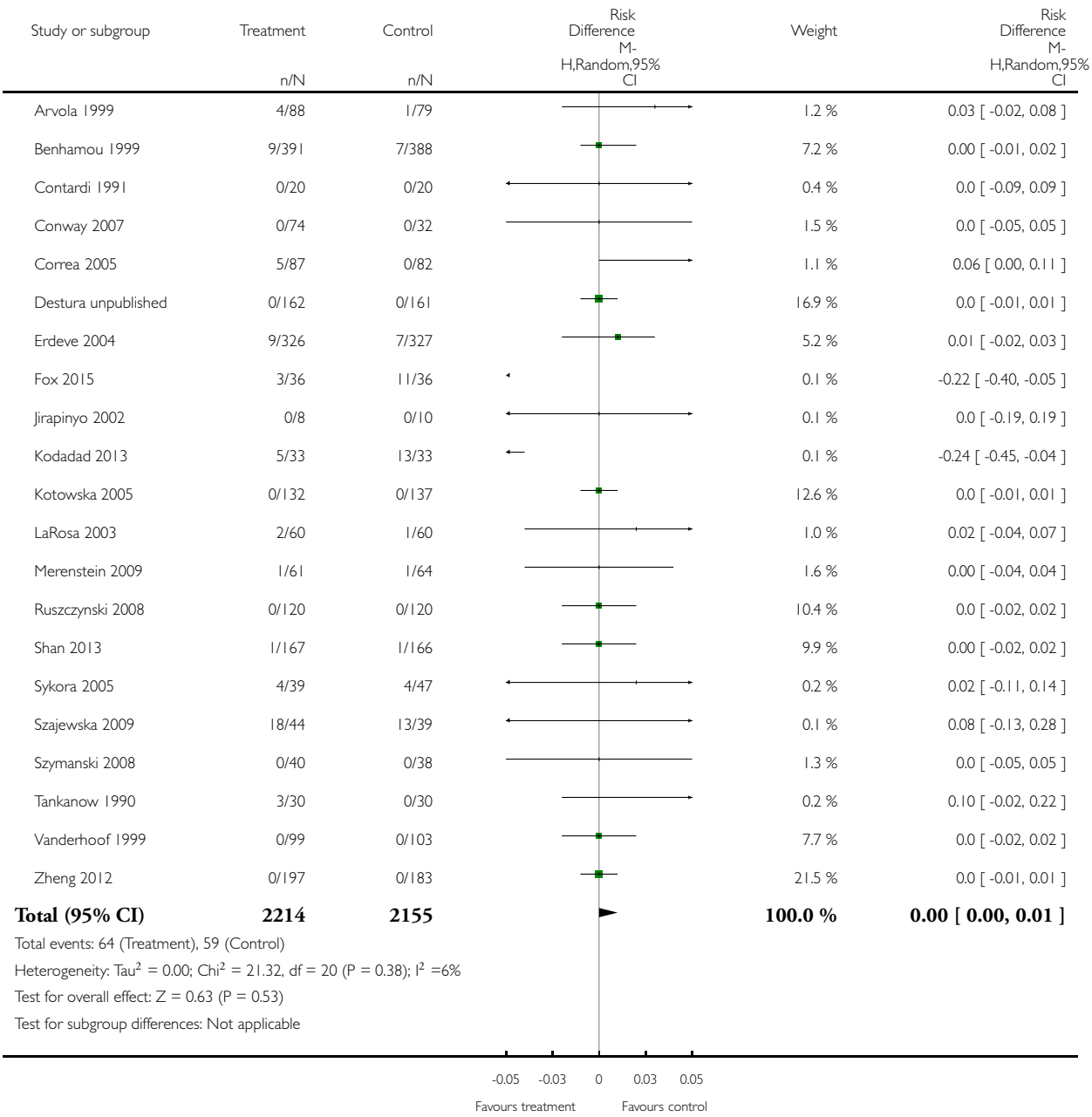
Test for subgroup differences: Not applicable

Analysis 1.15. Comparison 1 Probiotics versus control, Outcome 15 Adverse events: Same event rate assumptions analysis.

Review: Probiotics for the prevention of pediatric antibiotic-associated diarrhea

Comparison: 1 Probiotics versus control

Outcome: 15 Adverse events: Same event rate assumptions analysis



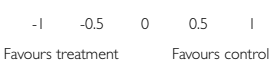
Analysis 1.16. Comparison 1 Probiotics versus control, Outcome 16 Adverse events: Risk of bias.

Review: Probiotics for the prevention of pediatric antibiotic-associated diarrhea

Comparison: 1 Probiotics versus control

Outcome: 16 Adverse events: Risk of bias

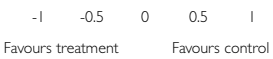
Study or subgroup	Treatment n/N	Control n/N	Risk Difference M-H,Random,95% CI	Weight	Risk Difference M-H,Random,95% CI
1 Low RoB					
Correa 2005	5/80	0/77		1.8 %	0.06 [0.00, 0.12]
Fox 2015	3/34	11/36		0.2 %	-0.22 [-0.40, -0.04]
Kotowska 2005	0/119	0/127		13.6 %	0.0 [-0.02, 0.02]
Merenstein 2009	1/57	1/60		2.6 %	0.00 [-0.05, 0.05]
Ruszczynski 2008	0/120	0/120		13.2 %	0.0 [-0.02, 0.02]
Sykora 2005	4/39	4/47		0.4 %	0.02 [-0.11, 0.14]
Szajewska 2009	18/35	13/32		0.1 %	0.11 [-0.13, 0.35]
Szymanski 2008	0/40	0/38		2.4 %	0.0 [-0.05, 0.05]
Vanderhoof 1999	0/93	0/95		9.8 %	0.0 [-0.02, 0.02]
Subtotal (95% CI)	**617**	**632**		**44.1 %**	**0.00 [-0.01, 0.02]**
Total events: 31 (Treatment), 29 (Control)					
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 11.12$, df = 8 (P = 0.19); $I^2 = 28\%$					
Test for overall effect: Z = 0.36 (P = 0.72)					
2 High/Unclear					
Conway 2007	0/74	0/32		2.7 %	0.0 [-0.05, 0.05]
Destura unpublished	0/162	0/161		17.6 %	0.0 [-0.01, 0.01]
Jirapinyo 2002	0/8	0/10		0.2 %	0.0 [-0.19, 0.19]
Kodadad 2013	5/33	13/33		0.1 %	-0.24 [-0.45, -0.04]
Shan 2013	0/139	0/144		15.7 %	0.0 [-0.01, 0.01]
Tankanow 1990	3/15	0/23		0.1 %	0.20 [-0.01, 0.41]
Zheng 2012	0/193	0/179		19.5 %	0.0 [-0.01, 0.01]
Subtotal (95% CI)	**624**	**582**		**55.9 %**	**0.00 [-0.01, 0.01]**



(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	Treatment n/N	Control n/N	Risk Difference M-H,Random,95% CI	Weight	Risk Difference M-H,Random,95% CI
Total events: 8 (Treatment), 13 (Control)					
Heterogeneity: Tau² = 0.00; Chi² = 13.23, df = 6 (P = 0.04); I² =55%					
Test for overall effect: Z = 0.03 (P = 0.98)					
Total (95% CI)	**1241**	**1214**		**100.0 %**	**0.00 [-0.01, 0.01]**
Total events: 39 (Treatment), 42 (Control)					
Heterogeneity: Tau² = 0.00; Chi² = 20.71, df = 15 (P = 0.15); I² =28%					
Test for overall effect: Z = 0.20 (P = 0.84)					
Test for subgroup differences: Chi² = 0.07, df = 1 (P = 0.79), I² =0.0%					



Analysis 1.17. Comparison 1 Probiotics versus control, Outcome 17 Mean duration of diarrhea: Complete case.

Review: Probiotics for the prevention of pediatric antibiotic-associated diarrhea

Comparison: 1 Probiotics versus control

Outcome: 17 Mean duration of diarrhea: Complete case

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Arvola 1999	60	4 (1.5)	59	4 (1.5)		21.1 %	0.0 [-0.54, 0.54]
Correa 2005	80	3.92 (2.47)	77	5 (2.8)		16.9 %	-1.08 [-1.91, -0.25]
Destura unpublished	162	4 (3.46)	161	3.86 (2.26)		19.7 %	0.14 [-0.50, 0.78]
LaRosa 2003	56	0.7 (1.4)	54	1.6 (2)		19.6 %	-0.90 [-1.55, -0.25]
Vanderhoof 1999	93	4.7 (1.5)	95	5.88 (1.5)		22.7 %	-1.18 [-1.61, -0.75]
Total (95% CI)	**451**		**446**			**100.0 %**	**-0.60 [-1.18, -0.02]**
Heterogeneity: Tau² = 0.34; Chi² = 18.97, df = 4 (P = 0.00080); I² =79%							
Test for overall effect: Z = 2.03 (P = 0.043)							
Test for subgroup differences: Not applicable							

Analysis 1.18. Comparison 1 Probiotics versus control, Outcome 18 Mean stool frequency: Complete case.

Review: Probiotics for the prevention of pediatric antibiotic-associated diarrhea

Comparison: 1 Probiotics versus control

Outcome: 18 Mean stool frequency: Complete case

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Arvola 1999	59	5 (1.5)	60	5 (1.5)		16.3 %	0.0 [-0.54, 0.54]
Contardi 1991	20	2 (0.3)	20	2.7 (0.5)		27.3 %	-0.70 [-0.96, -0.44]
Szymanski 2008	40	1 (0.4)	38	1.3 (0.6)		28.5 %	-0.30 [-0.53, -0.07]
Vanderhoof 1999	93	1.5 (0.8)	95	1.59 (0.88)		27.9 %	-0.09 [-0.33, 0.15]
Total (95% CI)	**212**		**213**			**100.0 %**	**-0.30 [-0.60, 0.00]**

Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 13.39$, df = 3 (P = 0.004); $I^2 = 78\%$

Test for overall effect: Z = 1.96 (P = 0.050)

Test for subgroup differences: Not applicable

APPENDICES

Appendix 1. Table: Subgroup Credibility: Definition of Diarrhea

Table 1. Criteria for judging the credibility of subgroup analyses: Probiotic Definition

Design		
Is the subgroup variable a characteristic measured at baseline or after randomisation?	Yes, baseline	
Is the effect suggested by comparisons within rather than between studies?	No, but Fox 2015 used multiple definitions showing differing results depending on definition	
Was the hypothesis specified *a priori*?	Yes	
Was the direction of the subgroup effect specified *a priori*?	Yes	
Was the subgroup effect one of a small number of hypothesised effects tested?	Yes (1 of 5 *a priori* and 9 subgroups overall)	
Analysis		
Does interaction test suggest low likelihood that chance explains the apparent subgroup effect?	Yes (P = 0.0009). When Fox 2015 is limited to a single definition the test for interaction is still statistically significant (P = 0.02)	
Is the significant subgroup effect independent?	Probably yes, additional 8 subgroup analyses were not statistically significant and appear to not be related to the definition based effect sizes	
Context		
Is the size of the subgroup effect large?	Yes. The variation in effect sizes range from RR 0.08 to 0.96 depending on definition	
Is the interaction consistent across studies?	No, there is no clear pattern as one moves from strict to more conservative definitions of diarrhea	
Is the interaction consistent across closely related outcomes within the study?	Unable to judge as both closely related outcomes (stool frequency and stool duration) are used in the various definitions	
Is there indirect evidence that supports the hypothesised interaction (biological rationale)?	Yes, the stricter definitions may include more severe AAD which may arguably not respond to probiotics	

See: Sun X, Briel M, Walter S, Guyatt GH. Is a subgroup effect believable? Updating criteria to evaluate the credibility of subgroup analyses. BMJ 2010 Mar 30;340:c117.

WHAT'S NEW

Last assessed as up-to-date: 24 November 2014.

Date	Event	Description
22 December 2015	Amended	Correction of typo

HISTORY

Protocol first published: Issue 3, 2004

Review first published: Issue 2, 2007

Date	Event	Description
24 November 2014	New citation required and conclusions have changed	Substantively updated review with new conclusions and new authors
24 November 2014	New search has been performed	New search, new studies added

CONTRIBUTIONS OF AUTHORS

This version of the review:

Joshua Z. Goldenberg: Concept, screening, inclusion/exclusion, data extraction, quality assessment, data analysis, manuscript preparation, administrative and technical support

Lyubov Lytvyn: Screening, inclusion/exclusion, data extraction, quality assessment

Justin Steurich: Screening, inclusion/exclusion, data extraction, quality assessment

Sanjay Mahant: data analysis, manuscript preparation

Patricia C. Parkin: data analysis, manuscript preparation

Bradley C. Johnston: Concept, developed review protocol, search strategy, screening, inclusion/exclusion, data extraction, quality assessment, data analysis, manuscript preparation, administrative and technical support

Previous versions of the review:

Please refer to the 2007 and 2011 version of the Cochrane review for previous contributions.

DECLARATIONS OF INTEREST

Joshua Z Goldenberg has no known conflicts to declare.

Lyubov Lytvyn has no known conflicts to declare.

Justin Steurich has no known conflicts to declare.

Patricia Parkin is a co-investigator with Dr. Bradley Johnston who received funds from BioK+ to conduct a non-interventional prospective cohort study to document the incidence of AAD.

Sanjay Mahant is a co-investigator with Dr. Bradley Johnston who received funds from BioK+ to conduct a non-interventional prospective cohort study to document the incidence of AAD.

Bradley C Johnston received seed funds in 2013 from BioK+, a manufacturer of an *L. acidophilus* cocktail containing 3 strains, to assess the risk of antibiotic-associated diarrhea in hospitalized children. This was a prospective cohort study to evaluate the natural history of children prescribed antibiotics and did not involve the administration of probiotics.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Hospital for Sick Kids Foundation, Toronto, Ontario, Canada.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Post hoc subgroup analyses

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Bacterial Agents [*adverse effects]; Diarrhea [chemically induced; *prevention & control]; Probiotics [*therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Adolescent; Child; Child, Preschool; Female; Humans; Infant; Male