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[Intervention Review]

Probiotics for the prevention of pediatric antibiotic-associated diarrhea

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ABSTRACT

Background

Antibiotics alter the microbial balance commonly resulting in antibiotic-associated diarrhea (AAD). Probiotics may prevent AAD via providing gut barrier, restoration of the gut microflora, and other potential mechanisms of action.

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, and the Web of Science (inception to 28 May 2018) were searched along with registers including the ISRCTN and Clinicaltrials.gov. We also searched the NICE Evidence Services database as well as reference lists from relevant articles.

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, and risk of bias assessment were conducted independently by two authors. Dichotomous data (incidence of AAD, adverse events) were combined using a pooled risk ratio (RR) or risk difference (RD), and continuous data (mean duration of diarrhea) as mean difference (MD), along with corresponding 95% confidence interval (95% CI). We calculated the number needed to treat for an additional beneficial outcome (NNTB) where appropriate. For studies reporting on microbiome characteristics using heterogeneous outcomes, we describe the results narratively. The certainty of the evidence was evaluated using GRADE.

Main results

Thirty-three studies (6352 participants) were included. Probiotics assessed included *Bacillus spp., Bifidobacterium spp., Clostridium butyricum*, *Lactobacilli spp.*, *Lactococcus spp., Leuconostoc cremoris*, *Saccharomyces spp.,* or*Streptococcus spp.,* alone or in combination. The risk of bias was determined to be high in 20 studies and low in 13 studies. Complete case (patients who did not complete the studies were not included in the analysis) results from 33 trials reporting on the incidence of diarrhea show a precise benefit from probiotics compared to active, placebo or no treatment control.

After 5 days to 12 weeks of follow-up, the incidence of AAD in the probiotic group was 8% (259/3232) compared to 19% (598/3120) in the control group (RR 0.45, 95% CI 0.36 to 0.56; I^2 = 57%, 6352 participants; NNTB 9, 95% CI 7 to 13; moderate certainty evidence). Nineteen studies had loss to follow-up ranging from 1% to 46%. After making assumptions for those lost, the observed benefit was still statistically significant using an extreme plausible intention-to-treat (ITT) analysis, wherein the incidence of AAD in the probiotic group was 12% (436/3551) compared to 19% (664/3468) in the control group (7019 participants; RR 0.61; 95% CI 0.49 to 0.77; P <0.00001; I^2 = 70%). An a priori available case subgroup analysis exploring heterogeneity indicated that high dose (≥ 5 billion CFUs per day) is more effective than low probiotic dose (< 5 billion CFUs per day), interaction P value = 0.01. For the high dose studies the incidence of AAD in the probiotic group was 8% (162/2029) compared to 23% (462/2009) in the control group (4038 participants; RR 0.37; 95% CI 0.30 to 0.46; P = 0.06; moderate certainty evidence). For the low dose studies the incidence of AAD in the probiotic group was 8% (97/1155) compared to 13% (133/1059) in the control group (2214 participants; RR 0.68; 95% CI 0.46 to 1.01; P = 0.02). Again, assumptions for loss to follow-up using an extreme plausible ITT analysis was statistically significant. For high dose studies the incidence of AAD in the probiotic group was 13% (278/2218) compared to 23% (503/2207) in control group (4425 participants; RR 0.54; 95% CI 0.42 to 0.70; P <0.00001; I^2 = 68%; moderate certainty evidence).

None of the 24 trials (4415 participants) that reported on adverse events reported any serious adverse events attributable to probiotics. Adverse event rates were low. After 5 days to 4 weeks follow-up, 4% (86/2229) of probiotics participants had an adverse event compared to 6% (121/2186) of control participants (RD 0.00; 95% CI -0.01 to 0.01; P < 0.00001; I^2 = 75%; low certainty evidence). Common adverse events included rash, nausea, gas, flatulence, abdominal bloating, and constipation.

After 10 days to 12 weeks of follow-up, eight studies recorded data on our secondary outcome, the mean duration of diarrhea; with probiotics reducing diarrhea duration by almost one day (MD -0.91; 95% CI -1.38 to -0.44; P <0.00001; low certainty evidence). One study reported on microbiome characteristics, reporting no difference in changes with concurrent antibiotic and probiotic use.

Authors' conclusions

The overall evidence suggests a moderate protective effect of probiotics for preventing AAD (NNTB 9, 95% CI 7 to 13). Using five criteria to evaluate the credibility of the subgroup analysis on probiotic dose, the results indicate the subgroup effect based on high dose probiotics (≥ 5 billion CFUs per day) was credible. Based on high-dose probiotics, the NNTB to prevent one case of diarrhea is 6 (95% CI 5 to 9). The overall certainty of the evidence for the primary endpoint, incidence of AAD, based on high dose probiotics was moderate due to the minor issues with risk of bias and inconsistency related to a diversity of probiotic agents used. Evidence also suggests that probiotics may moderately reduce the duration of diarrhea, a reduction by almost one day. The benefit of high dose probiotics (e.g. *Lactobacillus rhamnosus* or*Saccharomyces boulardii*) needs to be confirmed by a large well-designed multi-centered randomized trial. It is premature to draw firm conclusions about the efficacy and safety of 'other' probiotic agents as an adjunct to antibiotics in children. Adverse event rates were low and no serious adverse events were attributable to probiotics. Although no serious adverse events were observed among inpatient and outpatient children, including small studies conducted in the intensive care unit and in the neonatal unit, observational studies not included in this review have reported serious adverse events in severely debilitated or immuno-compromised children with underlying risk factors including central venous catheter use and disorders associated with bacterial/fungal translocation.

PLAIN LANGUAGE SUMMARY

Probiotics for the prevention of 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 May 28, 2018.

What did the researchers find?

Thirty-three studies were reviewed and provide the best available evidence. The studies tested 6352 children (3 days 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 5 days to 12 weeks. Analyses showed that probiotics are effective for preventing AAD. The incidence of AAD in the probiotic

group was 8% (259/3232) compared to 19% (598/3120) in the control group, demonstrating a moderate reduction (11% fewer will suffer diarrhea). For every 9 children treated, probiotics will prevent one case of diarrhea. Further, evidence suggests that higher dose probiotics (≥ 5 billion CFUs per day) reduce the incidence of AAD. Eight per cent (162/2029) of the high dose probiotics group had AAD compared to 23% (462/2009) in the control group, demonstrating a moderate to large reduction (15% fewer suffer diarrhea). Probiotics were generally well tolerated, and minor side effects (e.g. rash, nausea, gas, flatulence, abdominal bloating, constipation) occurred infrequently. . Evidence suggested that probiotics are effective for a moderate reduction in duration of diarrhea (almost one day). Among the various probiotics evaluated, *Lactobacillus rhamnosus* or *Saccharomyces boulardii* at 5 to 40 billion colony forming units/day appear most 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 mostly otherwise healthy children who participated in the studies, serious side effects have been reported in observational studies not included in this review, including 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).

Summary of findings for the main comparison. Probiotics as an adjunct to antibiotics for the prevention of antibiotic-associated diarrhea in children

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

Patient or population: Children receiving antibiotic treatment between 4 and 28 days duration for a variety of infections

Settings: Inpatient and outpatient

Intervention: Probiotics treatment with either *Bacillus spp.*, *Bifidobacterium spp.*, *Clostridium butyricum spp.*, *Lactobacilli spp.*, *Lactococcus spp.*, *Leuconostoc cremoris spp.*, *Saccharomyces spp.*, or *Streptococcus spp.*, alone or in combination

Comparison: Control (placebo or non-active control)

Outcomes	Anticipated absolute effects * (95% CI)			Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Baseline risk	Corresponding risk					
	Risk in Control	Risk with Probiotics	Risk Difference				
Incidence of AAD Follow-up: 5 days to 12 weeks	**190 per 1000**[1]	**86 per 1000** (68 to 106)	**104 fewer AAD cases per 1000** (84 fewer to 122 fewer)	**RR 0.45** (0.36 to 0.56)	6352 (33 studies)	⊕⊕⊕⊖ **Moderate**[2.3.4]	
Incidence of AAD: Probiotic dose (≥5 billion CFUs of probiotics/day) Follow-up: 5 days to 12 weeks	**190 per 1000**[1]	**70 per 1000** (57 to 87)	**120 fewer AAD cases per 1000** (103 fewer to 133 fewer)	**RR 0.37** (0.30 to 0.46)	4038 (20 studies)	⊕⊕⊕⊖ **Moderate**[5.6]	Based on our a priori subgroup analyses, high-dose probiotics (≥5 billion CFUs/day) are most effective Low dose probiotics (<5 billion CFUs of probiotics per day) were not as effective as high dose probiotics (RR 0.68, 95% CI 0.46 to 1.01; low certainty evidence)
Adverse events Follow-up: 5 days to 4 weeks	**55 per 1000**[7]	**39 per 1000** (25 to 61)	**16 fewer adverse events per 1000**	**RD -0.00** (-0.01 to 0.01)	4415 (24 studies)	⊕⊕⊖⊖ **Low**[8.9.10.11]	

		(6 more to 30 fewer)			
Duration of diarrhea (days) Follow-up: 10 days to 12 weeks		**MD 0.91 fewer** (1.38 fewer to 0.44 fewer)		1263 (8 studies)	⊕⊕⊖⊖ **Low**[12,13]
Microbiome characteristics Follow-up: one day to one month after cessation of antibiotic therapy				40 (1 study)	⊕⊖⊖⊖ **Very low**[14,15]

*The basis for the **baseline risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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; **MD**: Mean difference; **RD**: Risk difference; **RR:** Risk Ratio
AAD: antibiotic-associated diarrhea;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Baseline/control group risk estimates come from pooled estimates of control group among 33 included studies.

[2] 20 of 33 studies were rated as high risk of bias to due to issues with lack of blinding, or lack of concealment of allocation, or loss to follow-up (LTFU) or industry sponsorship. Loss to follow-up was substantial (>20%) in 6 studies. In particular, LTFU was 46.4% (King 2010) and 36.6% in two small studies (Tankanow 1990), respectively; and 29% in two additional studies (Arvola 1999; Erdeve 2004), one of which was the largest eligible trial included in our review (n=653) (Erdeve 2004). However, a test for interaction between low risk of bias trials and high or unclear risk of bias trials was not statistically significant (P = 0.30). Further, we conducted a sensitivity analysis wherein we made assumptions about the outcomes for patients that went missing and found similar clinically important results (RR 0.61; 95% CI 0.49 to 0.77).

[3] I^2 is 57% with a P value less than 0.0001 suggesting substantial heterogeneity. We explored the heterogeneity based on nine a priori subgroups, with probiotic dose (high versus low) demonstrating a significant subgroup to help explain the moderate heterogeneity observed. We tested the credibility of this subgroup using published criteria and determined that the subgroup demonstrating increased efficacy of high probiotic dose (≥5 billion CFUs/day) is credible, thus we present the results for this subgroup analysis as separate row in the table.

[4] Regarding inconsistency (I^2 is 57%), given the variability in probiotic species and/or strains used, a priori we planned a subgroup analysis to explore if there were important differences in treatment effect between products with specific species and/or strains. Our subgroup analysis demonstrated no statistically significant difference between products based on our test of interaction (P = 0.94), demonstrating that variability in products used was a minor issue and we therefore did not rate down. However for AAD, given the minor issues with both risk of bias and inconsistency, we rated down once from high to moderate quality evidence.

[5] 13 of 20 studies were rated as high risk of bias due to lack of concealment of allocation, blinding, LTFU or other bias (such as sponsored by industry). 7 of 20 studies were open label or not blinded. Loss to follow-up was substantial (>20%) in 3 studies. In particular, LTFU was 46.4% in a small study (King 2010) and 29% in two studies that were moderate in

size (Arvola 1999) and large in size (Erdeve 2004), respectively. However, our a priori subgroup analysis on risk of bias demonstrated no statistically significant difference between studies at high risk versus low risk of bias (P = 0.30). Therefore we judged risk of bias is a minor issue and we did not rate down.

[6] Regarding inconsistency (I^2 is 57%), given the variability in probiotic species and/or strains used, a priori we planned a subgroup analysis to explore if there were important differences in treatment effect between probiotic species/strains. Our subgroup analysis demonstrated no statistically significant difference between species/strains (P = 0.94), demonstrating that variability in products used was a minor issue and we therefore did not rate down. Given the minor issues with risk of bias and inconsistency, again for high dose probiotics (≥5 billion CFUs/day), we rated down once from high to moderate quality evidence.

[7] Baseline/control group risk estimates come from pooled estimates of control groups.

[8] Only 24 of 33 studies reported on adverse events, suggesting a selective reporting bias and we therefor rated down.

[9] The total number of events (207) is less than 400 suggesting issues with imprecision. However, imprecision is a minor issue as adverse events are more common in the placebo group and other more comprehensive reviews specific to probiotic safety in variety of clinical settings suggest that short-term use of probiotics is safe in otherwise healthy children, with no evidence to suggest a risk of sepsis in the general population.

[10] Regarding indirectness related to safety, numerous probiotic products and doses were evaluated amongst eligible trials. Overall for all studies there were more adverse events in the placebo group and we considered indirectness related to adverse events a minor issue.

[11] Regarding inconsistency related to the safety of probiotics, statistical tests show considerable heterogeneity (I^2 = 75% P<0.00001), possibly due to the variability in how adverse events were captured and defined across the eligible trials; we therefor rated down for serious inconsistency.

[12] 8 of 33 trials reported duration of diarrhea, suggesting a selective reporting bias and we rated down.

[13] We further rated down for inconsistency given the large statistical heterogeneity (I^2 = 84%), very low P value [P<0.00001]), and given that point estimates and confidence intervals vary considerably.

[14] Only 1 study with small sample size (n = 40) reported microbiome characteristics, suggesting very serious imprecision and the possibility of selective reporting. We therefore rated down twice for imprecision and once for selective reporting.

[15] Microbiome results are not of importance to patients and we rated down for indirectness. Further, the use of 16S rRNA gene sequences to study bacterial phylogeny and taxonomy has been by far the most common test and authors did not use other suggested methods for measuring microbiome characteristics, making the results difficult to summarize and interpret for clinicians (Janda 2007; Mclnnes 2010).

BACKGROUND

Description of the condition

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 (McFarland 2008; Owens 2008; Wistrom 2001). 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 (Arvola 1999; Berrington 2004). Reports in the general population indicate that the incidence of AAD ranges from 5 to 62%, occurring at any point from the initiation of therapy to two months after the end of treatment (LaRosa 2003; McFarland 1998; McFarland 2008; Wistrom 2001). The incidence of diarrhea in children receiving broad spectrum antibiotics has been reported in the range of 11 to 40% (Elstner 1983; Turck 2003). 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 (Bartlett 1978; McFarland 1998; McFarland 2008). *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.

Description of the intervention

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). 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*.

How the intervention might work

The rationale behind probiotic administration is based on re-inoculation and normalization of unbalanced indigenous microflora using specific probiotic strains.

Why it is important to do this review

Previously we demonstrated the efficacy and safety of probiotics used together with antibiotics for the prevention of AAD among 23 studies including 3938 otherwise healthy children (Goldenberg 2015). This review seeks to update our 2015 review, and to further explore the study setting (e.g. inpatient, outpatient) and intervention characteristics (e.g. dose, strain(s)) that may be most effective and safe, particularly given recent concerns about inadequate reporting on the safety of probiotics in randomized trials (Bafeta 2018; Suez 2018).

SAFETY OF PROBIOTICS

Based on the bulk of the literature, the safety of diverse probiotic interventions does not appear to be a concern in healthy individuals (Borriello 2003; Hammerman 2006; Hempel 2011; Whelan 2010). Infections (e.g. bacteremia, endocarditis, septicemia, pneumonia, deep abdominal abscesses) resulting from probiotic use have been reported in neonates, and in severely debilitated and immuno-compromised individuals (Hata 1988; Land 2005; Mackay 1999; McFarland 1998; Piarroux 1999; Rautio 1999; Salminen 1998; Salminen 2004; Saxelin 1996; Sussman 1986). 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; Cunningham-Rundles 2000; Lin 2005; Salminen 2004).

Five systematic reviews have addressed the safety of *Saccharomyces boulardii* (*S. boulardii)* and other probiotics (Didary 2014; Hassan 2018; Hempel 2011; McFarland 2010; Whelan 2010). In a review of the safety of various probiotic strains and doses reported in controlled clinical trials, as well as cases series and case reports from 1984 to 2013, Didary 2014 reported two bacteraemia cases associated with *Lactobacillus GG* and three fungemia cases in critically ill patients in the intensive care unit who had received *S. boulardii*. Hassan 2018 provided safety data for a total 2242 adults and children (25 studies) with cancer. An estimated 237 adverse events (AEs) occurred among those consuming probiotics and 314 AEs in those not consuming probiotics. Five case reports identified probiotic-related bacteraemia, fungaemia or positive blood cultures. However, based on these reviews it cannot be concluded with certainty that the observed infections were directly attributable to the probiotic consumed. 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 (traveler'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 larger 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 largest and most comprehensive systematic review to date, assessed the safety of probiotics in human participants (with no restrictions on participant type) 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) the results of 208 RCTs showed no 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).

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) impact microbiome characteristics.

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

The primary outcomes included:

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

Secondary outcomes

The secondary outcomes included:

1. Mean duration of diarrhea; and
2. Microbiome characteristics.

Search methods for identification of studies

Electronic searches

We searched the following databases from inception to 28 May 2018: The Cochrane Central Register of Controlled Trials (CENTRAL) on the Cochrane Library, MEDLINE, Embase, CINAHL, and Web of Science. There were no limitations on publication status or language. We also searched NICE Evidence Services (Formerly NHS Evidence) as well as ongoing trials through ClinicalTrials.gov and the ISRCTN (International Standard Randomized Controlled Trial Number Register). The search strategies are reported in Appendix 1.

Searching other resources

We searched the bibliographies of randomised controlled trials and review articles for additional studies not identified by the electronic searches.

Data collection and analysis

Selection of studies

Two authors (QG, CH) independently screened the search results using titles of papers, and when available, abstracts. The full-text of the selected articles was retrieved and independently assessed for inclusion by QG and CH according to pre-specified selection criteria. Disagreement was resolved by discussion and consensus. In the event of disagreement, a third author (BJ) was consulted.

Data extraction and management

Using a standardized data extraction form two authors (QG, CH) independently 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, and microbiome characteristics. For articles published in abstract form only, we obtained further information by contacting corresponding authors.

Assessment of risk of bias in included studies

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 independently evaluated by two authors (QG, CH) using the risk of bias instrument to assess each of the following domains: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other sources of bias (Hartling 2009). Disagreement was resolved by discussion or a third arbitrator. We assumed that studies that had three or more domains at high or unclear risk of bias were at high risk of bias overall.

Measures of treatment effect

Using a random-effects model, dichotomous data are presented as risk ratios (RR), and continuous data as mean difference (MD), along with corresponding 95% confidence interval (95% CI). Using control event risks from the included trials, the number needed to treat for an additional beneficial outcome (NNTB) or the number needed to treat for an additional harmful outcome (NNTH) was calculated for statistically significant dichotomous outcomes. Adverse events were summarized using risk difference (RD) since these events were rare.

Unit of analysis issues

If a trial had multiple intervention arms (such as two different strains compared to placebo), we combined the two probiotic arms to make a single pair wise comparison to avoid unit of analysis errors.

Dealing with missing data

When authors neglected to report PICO related items of interest, we contacted them via email. To assess the potential influence of missing outcome responses (e.g. children lost to follow-up), sensitivity analyses were applied for the primary outcomes, incidence of diarrhea and adverse events. Although many approaches exist for evaluating the sensitivity of results for missing outcome data (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). See sensitivity analysis section below.

Assessment of heterogeneity

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 explored including: a) inpatient versus outpatient, b) diagnosis, c) probiotic species or strain(s) (when two or more trials administered the same strains), d) single strain versus multi-strain probiotics, e) dosage of probiotic (≥5 billion colony forming units of live bacteria/yeast, <5 billion colony forming units of live bacteria/yeast), f) definition of diarrhea, g) diagnostic criteria for diarrhea (moderate diarrhea was assumed to be ≥ 3 watery/liquid stools per 24 hrs, whereas mild diarrhea was deemed to be 1 to 2 watery/liquid stools per 24 hrs), h) industry sponsorship, and i) quality criterion (i.e. risk of bias). We also explored heterogeneity with a *post hoc* subgroup based on age (0-2 years [≤24 months] versus more than 2 years of age or older [>24 months]).

Assessment of reporting biases

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).

Data synthesis

We conducted a meta-analysis as described in the measures of treatment effect and assessments of heterogeneity sections described in detail above.

We employed the GRADE system for rating overall certainty 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).

Subgroup analysis and investigation of heterogeneity

We investigated subgroups of interest as described in the 'assessment of heterogeneity' section, detailed above.

Sensitivity analysis

We conducted sensitivity analyses using a fixed-effect model as compared to random-effects, and we assessed the potential influence of missing participant outcome data as compared to a complete case analysis, with the latter described in 'dealing with missing data' section above.

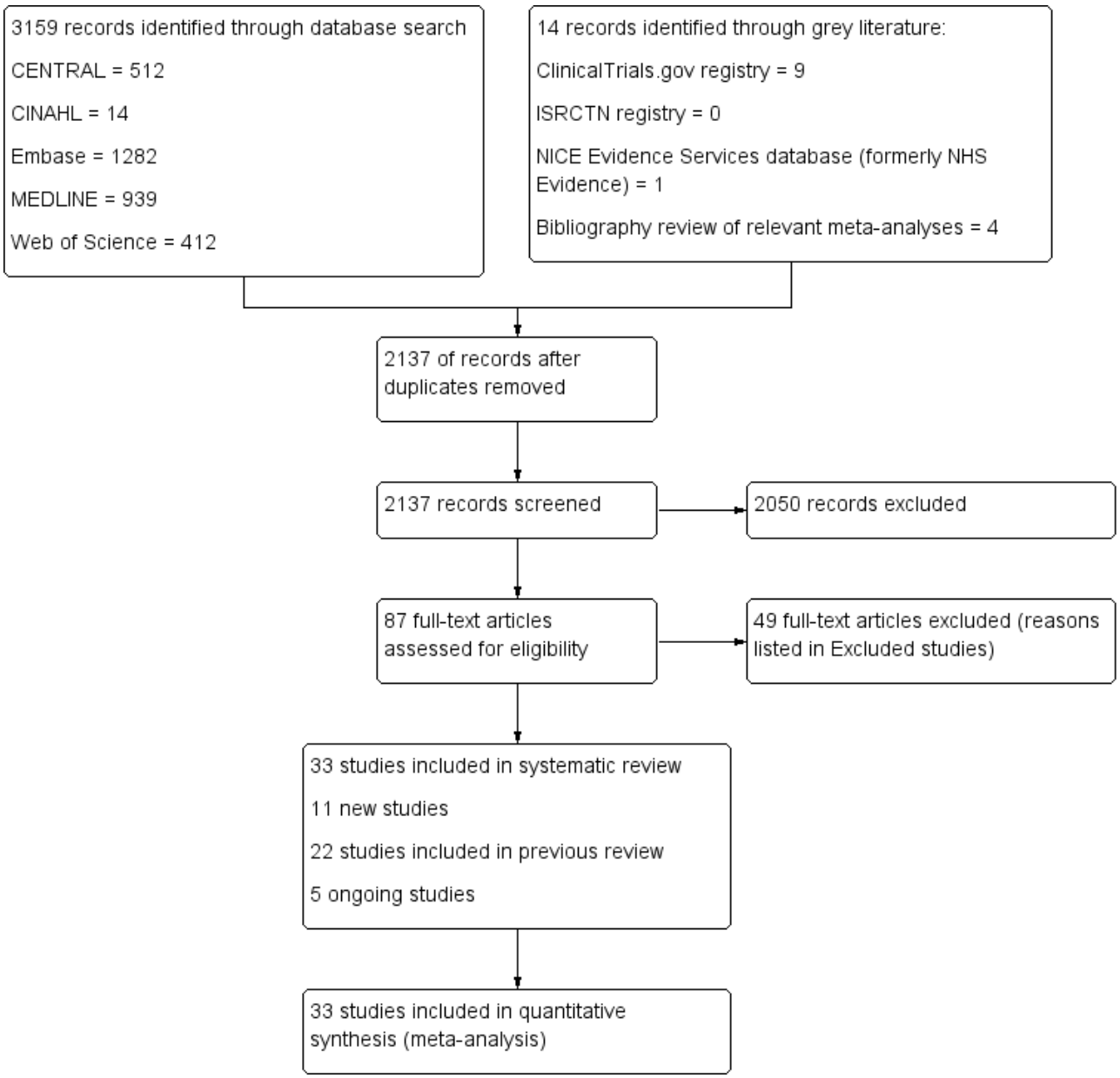
RESULTS

Description of studies

Results of the search

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). For this review update, we searched five primary electronic databases from inception to 28 May 2018. We identified a total of 3159 studies (Medline 939, EMBASE 1282, CENTRAL 512, CINAHL 14, Web of Science 412). Additionally, a grey literature search of the NICE Evidence Services database, ISRCTN and ClinicalTrials.gov registries, as well as bibliographic review of eligible randomized trials and meta-analyses identified an additional 14 relevant studies (See Figure 1).

Figure 1. Study flow diagram.



Of all of these studies, 1036 were identified as duplicates, leaving 2137 abstracts and titles identified as original publications. Independent review of these titles and abstracts identified 87 potentially relevant studies for full-text review. Three authors independently assessed these studies and identified 33 trials that met the inclusion criteria, eleven of which were new since the previous version of this review (Goldenberg 2015). Five ongoing studies were also identified. Excluded studies are described below.

Included studies

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 33 eligible studies included a total of 6352 patients (3232 treatment, 3120 controls). Patients in the trials were treated with antibiotics for upper and lower respiratory tract, or ear infections (Arvola 1999; Kotowska 2005; LaRosa 2003; Merenstein 2009; Peng 2014; Zheng 2012), *Helicobacter pylori* infection (Kodadad 2013; Saneeyan 2011; Szajewska 2009; Sykora 2005; Zhang 2015; Zhao 2014), mixed infections (Destura unpublished; Fox 2015; Georgieva 2015; Jindal 2017; Kolodziej 2018; Olek 2017; Ruszczynski 2008; Shan 2013; Szymanski 2008; Tankanow 1990; Vanderhoof 1999; Wan 2017; Zakordonets 2016), impetigo (Dharani 2017), hypospadias repair (Esposito 2017) 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 29 studies and consisted of: private primary care practices (Benhamou 1999; Conway 2007; Merenstein 2009; Olek 2017; Tankanow 1990; Vanderhoof 1999), hospitalized inpatients (Correa 2005; Esposito 2017; Georgieva 2015; Jirapinyo 2002; King 2010; Peng 2014; Szajewska 2009; Shan 2013; Wan 2017; Zakordonets 2016; Zheng 2012), an outpatient university teaching hospital (Arvola 1999; Dharani 2017; Jindal 2017; Kotowska 2005; Saneeyan 2011), and both inpatient and outpatient hospital populations (Destura unpublished; Kolodziej 2018; Zhao 2014). Three studies recruited from a hospital but it was unclear if the participants were inpatient or outpatient (Kodadad 2013; Sykora 2005; Zhang 2015). In addition to inpatient and outpatient hospital populations, Ruszczynski 2008 also enrolled from a private practice, and Szymanski 2008 also enrolled from outpatient clinics. King 2010 was the only trial which was conducted among hospitalized patients in the Intensive Care Unit.

Children enrolled were from families of diverse socioeconomic status, and included 17 countries: Poland (Kolodziej 2018; Kotowska 2005; Olek 2017; Ruszczynski 2008; Szymanski 2008; Szajewska 2009), the United States of America (King 2010; Merenstein 2009; Tankanow 1990; Vanderhoof 1999), China (Peng 2014; Shan 2013; Wan 2017; Zhang 2015; Zhao 2014; Zheng 2012), Iran (Kodadad 2013; Saneeyan 2011), Italy (Esposito 2017; LaRosa 2003), India (Dharani 2017; Jindal 2017), Finland (Arvola 1999), France (Benhamou 1999), England (Conway 2007), Australia (Fox 2015), Brazil (Correa 2005), the Philippines (Destura unpublished), Turkey (Erdeve 2004), Bulgaria (Georgieva 2015), Thailand (Jirapinyo 2002), Ukraine (Zakordonets 2016), and the Czech Republic (Sykora 2005). Children ranged from 3 days to 18 years of age. Twenty-six 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 2015), 9.1 years (Kodadad 2013), 1.3 years treatment and 1.2 years control (Esposito 2017), 8.5 years treatment and 8.6 years control (Zhang 2015), 11.1 days treatment and 10.9 days control (Peng 2014), 7 years treatment and 9 years control (Zhao 2014), 1.1 years (Wan 2017), 0.96 years treatment and 4.7 years control (King 2010), 5.1 years treatment and 5.2 years control (Olek 2017), 2.1 years treatment and 2.1 years control (Kolodziej 2018), 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). Three studies provided only the age range of enrolled participants: 3 to 14 years (Zakordonets 2016), 1 to 15 years (Dharani 2017), 6 months to 12 years (Jindal 2017), and 1 month to 3 years (Jirapinyo 2002). One study provided median age with a range: 7 years (range 1 to 15) (Szymanski 2008). Twenty-six studies included both males and females (2395 males and 1943 females), one study only included males (Esposito 2017) and seven studies did not state sufficient information regarding sex (Arvola 1999; Benhamou 1999; Conway 2007; Erdeve 2004; Jindal 2017; Jirapinyo 2002; Zhang 2015).

Interventions

Overall the trials provided between 3 and 30 days of antibiotic therapy. Most trials provided oral antibiotics.Two trials provided intravenous antibiotics to all patients (King 2010; Wan 2017). 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 five trials it was unclear what antibiotic or route was used (Conway 2007; Destura unpublished; Georgieva 2015; Merenstein 2009; Peng 2014). Six of 33 trials provided triple antibiotic therapy for *H. Pylori* and also followed patients for AAD (Kodadad 2013; Saneeyan 2011; Sykora 2005; Szajewska 2009; Zhang 2015; Zhao 2014).

One study provided oral amoxicillin alone (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) (Benhamou 1999; Correa 2005; Destura unpublished; Kotowska 2005), 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. Saneeyan 2011, Sykora 2005, Szajewska 2009, and Zhao 2014 provided all participants (n = 680) with amoxicillin and clarithromycin. Zhang 2015 provided participants with amoxicillin and clarithromycin or metronidazole if patients were allergic to penicillin. Dharani 2017 provided all participants (n = 100) with azithromycin, using a dose with 10 mg/kg/day, for 5 days. Esposito 2017 provided participants (84/90, 93%) with amoxicillin in combination with clavulanate, which the first therapeutic dose (50 mg/ kg) was given 30 min before surgery and a prophylactic dosage (20 mg/kg/day) was given after surgery. 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). Zakordonets 2016 provided all participants with Ceftriaxone (n = 40). 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). Jindal 2017 provided co-amoxyclav (n = 120, 25-45 mg/kg/day), cefpodoxime (n = 120, 10 mg/kg/day), cefdinir (n = 120, 14 mg/kg/day), cefixime (n = 120, 8 mg/kg/day), and cephalaxin (n = 120, 25 to 50 mg/kg/day). Zheng 2012 provided beta-lactams (n = 33), cephalosporins (n = 172), and macrolides (n = 22). Olek 2017 provided penicillins (n = 186), cephalosporins (n = 118), sulfometoksazole and trimethoprim (n = 32), and macrolides (n = 101). Kolodziej 2018 provided aminopenicillins (n = 63), cephalosporins 2nd generation (n = 149), cephalosporins third generation (n = 28), macrolides (n = 9), and lincosamides (n = 1).

Trials included treatment with either *Bacillus spp., Bifidobacterium spp., Clostridium butyricum, Lactobacilli spp.*, *Lactococcus spp., Leuconostoc cremoris*, *Saccharomyces spp.,* or*Streptococcus spp*. The species or strain(s) and daily dosage of the probiotic interventions included: *Lactobacillus GG,* 1 billion colony forming units (CFUs) bacteria/day (Szajewska 2009); *Lactobacillus GG*, 20 to 40 billion CFUs bacteria per day (Arvola 1999); *Lactobacillus GG,* 3 billion CFUs per day (King 2010);*Lactobacillus plantarum* DSM 9843, 10 billion CFUs per day (Olek 2017); *Lactobacillus reuteri* DSM 19738, 0.2 billion CFUs per day (Kolodziej 2018); *Lactobacillus rhamnosus* GG ATCC53103, 5 billion CFUs per day (Esposito 2017); *Lactobacillus GG* and inulin (a prebiotic), 10 to 20 billion CFUs 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*; *Bifidobacterium lactis* and *Streptococcus thermophilus*, 825 million CFUs bacteria/day (Correa 2005); *Bacillus clausii,* 4 billion CFUs bacteria/day (Destura unpublished);*Saccharomyces boulardii*, 5 billion CFUs yeast/day (Erdeve 2004; Peng 2014; Wan 2017); *Lactobacillus acidophilus* and *Bifidobacterium infantis*, dose not reported (Jirapinyo 2002); *Saccharomyces boulardii*, 10 billion CFUs of yeast/day (Jindal 2017; Kotowska 2005; Shan 2013; Zhang 2015; Zhao 2014); *Lactobacillus sporogenes* and fructo-oligosaccharide (a prebiotic); 5.5 billion CFUs 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 CFUs bacteria and yeast/day (Merenstein 2009); *Lactobacilluss rhamnosus,* 40 billion CFUs bacteria/day (Ruszczynski 2008);*Bifidobacterium longum* PL03,*Lactobacillus rhamnosus* KL53A, and *Lactobacillus plantarum* PL02, 200 million CFUs bacteria/day (Szymanski 2008); *Lactobacillus acidophilus* and *Lactobacillus bulgaricus*, 2 billion CFUs bacteria/day (Tankanow 1990); *Streptococcus thermophillus, Lactobacillus acidophilus, and Bifidobacteria anamalis* subsp. *lactus* or *Streptococcus thermophillus and Lactobacillus delbrueckii subsp. bulgaris,* 1 billion CFUs bacteria/day (Conway 2007); *Lactobacillus GG*, 5.2 billion CFUs/day; *Bifidobacterium bifidus*, 5.9 billion CFUs/day, *Lactobacillus acidophilus* 8.3 billion CFUs/day (Fox 2015); *Lactobacillus reuteri* 100 million CFUs/day (Georgieva 2015); *Lactobacillus acidophilus*, *Lactobacillus rhamnosus*, *Lactobacillus bulgaricus*, *Lactobacillus casei*, *Streptococcus thermophilus*, *Bifidobacterium infantis* and *Bifidobacterium breve* for a total of 1 billion CFUs/day (Kodadad 2013); *Lactobacilli* and *Lactococci*, *Bifidobacterium*, *propionate-oxidising bacteria* and *acetic acid bacteria*, 2 trillion CFUs/day (Zakordonets 2016); 50 million spores of *Lactobacillus sporegen* and 30 million spores of *Streptococcus faecalis*, 2 million spores of *Clostridium butyricum* and 1 million spores of *Bacillus mesentericus* , 166 million spores per day (Dharani 2017); *Lactobasillus casei*, *Lactobacillus acidophilus*, *Lactobasillus reuteri*, *Lactobasillus bulgaricus*, *Streptococcus*, *Bifidobacterium bifidum*, *Bifidobacterium infantis* for a total of 1 billion CFUs/day (Saneeyan 2011); *Lactobacillus casei* 10 billion CFUs/day (Sykora 2005); and finally *Clostridium Butyricum* and*Bifidobacterium* at 2.2 billion CFUs/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), eleven trials compared probiotics to no treatment (Destura unpublished; Dharani 2017; Erdeve 2004; Jindal 2017; Peng 2014; Shan 2013; Wan 2017; Zakordonets 2016; Zhang 2015; Zhao 2014; 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,and potato starch respectively (Esposito 2017; Kotowska 2005; Olek 2017; Ruszczynski 2008; Szajewska 2009). Three trials provided information about the placebo containing sugar, lactose, and glucose respectively (Esposito 2017; Jirapinyo 2002; Tankanow 1990). Kolodziej 2018 provided the information on the placebo which consisted of 'pharmaceutical grade medium chain triglycerides and sunflower oil together with pharmaceutical grade silicon dioxide.' King 2010 did not specify details of the placebo. 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 a formula containing vitamins, minerals and protein (Correa 2005).

Outcomes

Thirty-three studies (n = 6352) provided data on the incidence of diarrhea, 24 (n = 4415) reported on adverse events, and 8 studies (n = 1263) reported on the mean duration of diarrhea. Twenty-seven studies reported the definition of diarrhea or AAD. 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); at least two liquid stools per day (LaRosa 2003); two or more liquid stools per day on at least two occasions during the course of the study (Vanderhoof 1999; Wan 2017); three or more liquid/watery stools per day (Benhamou 1999; Correa 2005; Erdeve 2004; Esposito 2017; Jindal 2017; King 2010; Olek 2017; Peng 2014; Zhang 2015), three or more watery/loose/liquid stools per day for two consecutive days (Arvola 1999; Conway 2007; Kotowska 2005; Zakordonets 2016); 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 (Georgieva 2015; Ruszczynski 2008; Saneeyan 2011; Shan 2013; Szajewska 2009; Szymanski 2008). Two trials used different definitions of diarrhea (Fox 2015; Kolodziej 2018). One trial used various definitions of diarrhea which included (A) stool consistency ≥ 5 (as measured by the Bristol Stool Scale) and stool frequency ≥2/day for more than 2 days; (B) stool consistency ≥5 and stool frequency ≥3/day for more than 2 days; (C) stool consistency ≥ 6 and stool frequency ≥ 2/day for more than two days; and (D) stool consistency ≥ 6 and stool frequency ≥ 3/day for more than two days (Fox 2015). The second trial used three different definitions of diarrhea which included (A) ≥3 loose or watery stools per day for a minimum of 48 hours (strictest definition); (B) ≥3 loose or watery stools per day for a minimum of 24 hours; and (C) ≥2 loose or watery stools per day for a minimum of 24 hours (Kolodziej 2018). One study defined diarrhea as two or more bowel movements over the patient's baseline number of bowel movements (Zheng 2012).

Five studies reported on viral and bacterial analysis of fecal samples to exclude other causes of diarrhea (Arvola 1999; Destura unpublished; Kolodziej 2018; Kotowska 2005; Wan 2017). 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) and one study reported fecal microflora compositional three different time points (Zakordonets 2016). Three trials reported on frequencies of retroviral diarrhea, salmonella diarrhea, shigella diarrhea and *C. difficile* diarrhea (Kolodziej 2018; Kotowska 2005; Ruszczynski 2008). 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, hospitalisation of outpatients, or discontinuation of antibiotic treatment (Kolodziej 2018; Ruszczynski 2008; Szymanski 2008). Additionally, six studies reported on *H. pylori* outcomes such as positive rapid urea test, positive histopathology for *H. pylori*, and positive C13 urea breath test (Kodadad 2013; Saneeyan 2011; Sykora 2005; Szajewska 2009; Zhang 2015; Zhao 2014). No studies reported on cost-effectiveness related to absenteeism from the workplace, daycare or school between treatment and control groups.

Excluded studies

Forty-nine studies were excluded for not meeting the inclusion criteria. Reasons for exclusion are listed in the Characteristics of excluded studies tables.

Risk of bias in included studies

Loss to follow-up was substantial (i.e. > 20%) in 6/33 trials reporting on the incidence of diarrhea (Arvola 1999; Benhamou 1999; Erdeve 2004; King 2010; Szajewska 2009; Tankanow 1990). In particular, LTFU was 46% in King 2010, 37% in Tankanow 1990 and 29% in Arvola 1999. Ten trials provided a flow diagram to track participants some of which included details regarding drop-outs (Conway 2007; Kodadad 2013; Kolodziej 2018; Kotowska 2005; Merenstein 2009; Olek 2017; Ruszczynski 2008; Szajewska 2009; Szymanski 2008; Zhang 2015). All studies were randomized parallel group designs. Twenty-one studies reported using a 'double-blind' procedure. The risk of bias assessment determined that patients in the Conway 2007 and Tankanow 1990 studies were likely unblinded during treatment. Six trials were open label (Destura unpublished; Jindal 2017; Shan 2013; Zakordonets 2016; Zhang 2015; Zheng 2012). The validated risk of bias instrument categorizes risk into three categories: high risk of bias, low risk of bias and unclear. Thirteen trials were categorized as low risk (Destura unpublished; Fox 2015; Georgieva 2015; Kodadad 2013; Kolodziej 2018; Kotowska 2005; LaRosa 2003; Merenstein 2009; Olek 2017; Ruszczynski 2008; Sykora 2005; Szajewska 2009; Szymanski 2008) and 20 trials were categorized as high risk (Arvola 1999; Benhamou 1999; Conway 2007; Correa 2005; Dharani 2017; Erdeve 2004; Esposito 2017; Jindal 2017; Jirapinyo 2002; King 2010; Peng 2014; Saneeyan 2011; Shan 2013; Tankanow 1990; Vanderhoof 1999; Wan 2017; Zakordonets 2016; Zhang 2015; Zhao 2014; 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.

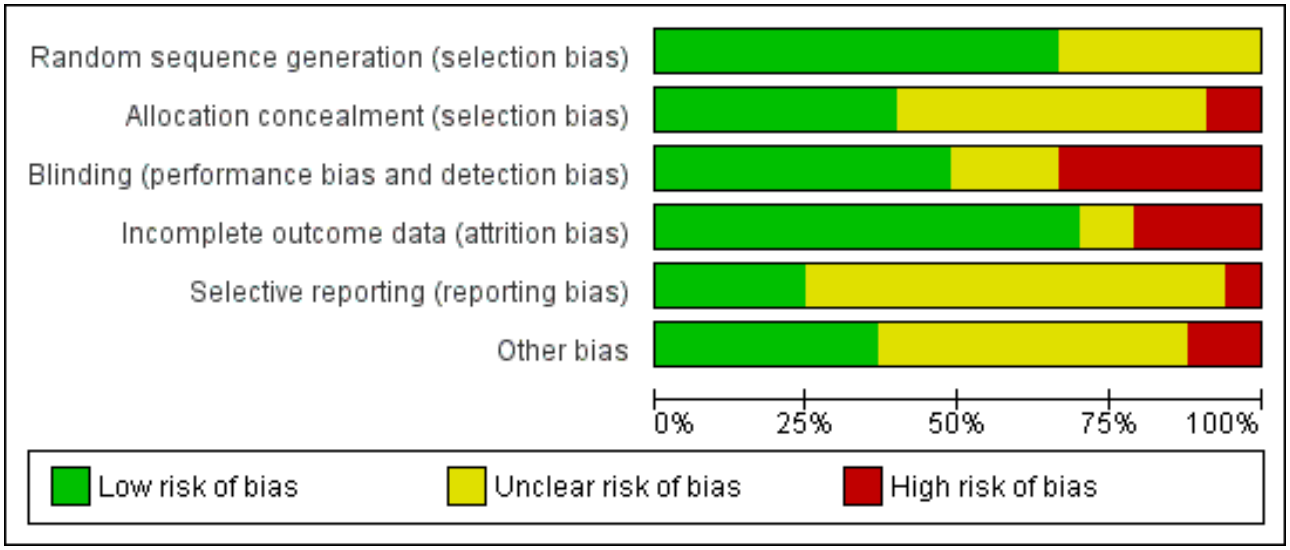


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

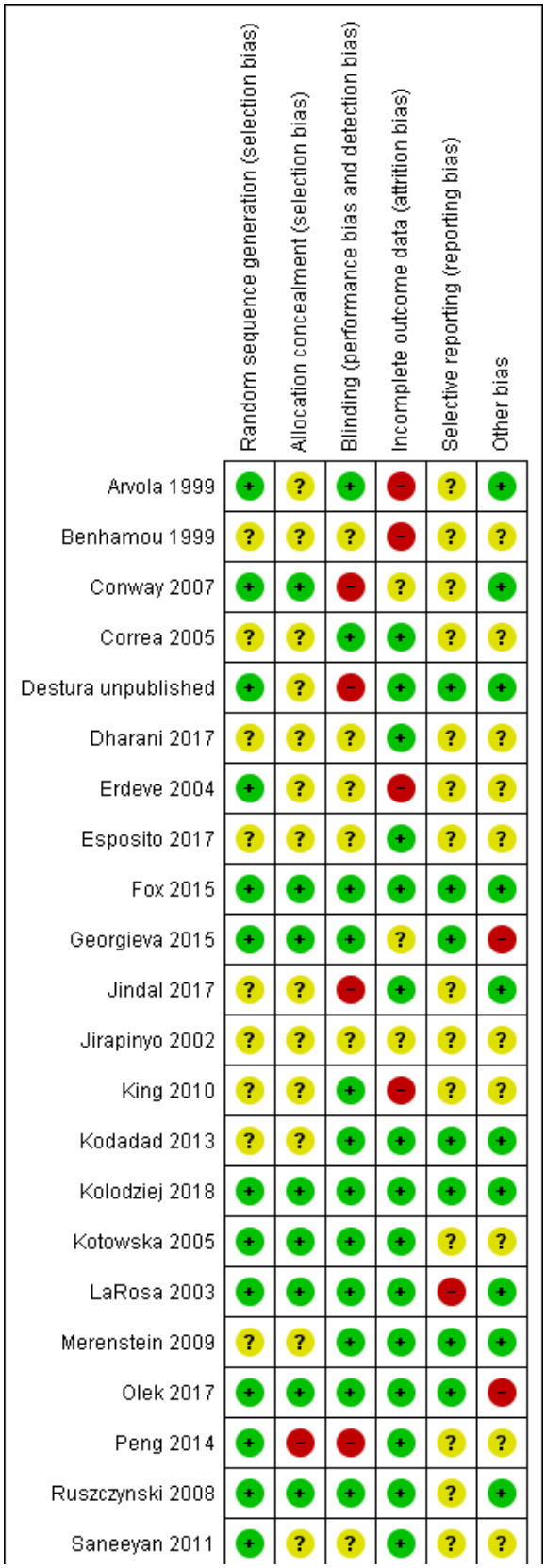
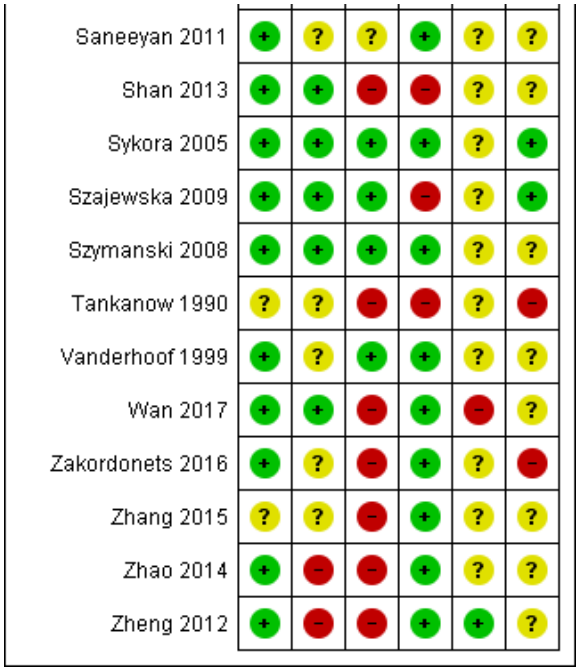


Figure 3. (Continued)



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. Thirty-three studies (n = 6352) reported on the incidence of diarrhea. Using an complete case (i.e. patients who did not complete the studies were not included in the analysis) approach as the primary analysis, seven placebo-controlled studies showed probiotics may reduce (P < 0.05) the incidence of AAD (Esposito 2017; Fox 2015; Kotowska 2005; LaRosa 2003; Ruszczynski 2008; Saneeyan 2011; Vanderhoof 1999); one active-controlled study (formula) suggested probiotics may reduce the incidence of AAD (Correa 2005), and eight 'no treatment-control' study demonstrated that probiotics may reduce the incidence of AAD (Erdeve 2004; Jindal 2017; Peng 2014; Shan 2013; Wan 2017; Zhang 2015; Zhao 2014; Zheng 2012). Twelve placebo-controlled studies (Arvola 1999; Georgieva 2015; Jirapinyo 2002; King 2010; Kodadad 2013; Kolodziej 2018; Merenstein 2009; Olek 2017; Sykora 2005; Szajewska 2009; Szymanski 2008; Tankanow 1990), four no treatment-control studies (Conway 2007; Destura unpublished; Dharani 2017; Zakordonets 2016), and one active-control (diosmectite) study (Benhamou 1999), showed no difference in the incidence of AAD. The overall pooled results using a complete case analysis showed that the use of probiotics probably produce a reduction in the incidence of AAD. After 5 days to 12 weeks of follow-up, the incidence of AAD in the probiotic group was 8% (259/3232) compared to 19% (598/3120) in the active, placebo or no treatment control group (6352 participants; RR 0.45; 95% CI 0.36 to 0.56; P < 0.00001; random-effects). However, substantial heterogeneity was detected (P < 0.00001) and this was moderate with respect to per cent variability due to between (or inter -) study variability (I^2 = 57%) (Higgins 2003). A GRADE analysis indicated that the overall quality of evidence for the outcome incidence of diarrhea was moderate due to minor issues with risk of bias and inconsistency (see Summary of findings for the main comparison).

Adverse events

None of the studies specifically defined adverse events a priori. Among 33 included studies, 25 followed and reported on adverse events including 13 studies reporting that no adverse events were observed (Conway 2007; Destura unpublished; Jindal 2017; Jirapinyo 2002; King 2010; Kotowska 2005; Ruszczynski 2008; Shan 2013; Szymanski 2008; Vanderhoof 1999; Wan 2017; Zakordonets 2016; Zheng 2012), and twelve trials reported a variety of adverse events, typically mild to moderate in nature (Correa 2005; Dharani 2017; Fox 2015; Kodadad 2013; Kolodziej 2018; Merenstein 2009; Olek 2017; Peng 2014; Sykora 2005; Szajewska 2009; Tankanow 1990; Zhao 2014). Among the 12 studies having reported specific adverse events, 11 reported incidence rates while 1 reported a rate ratio (Zhao 2014). For the purpose of meta-analysis, we only included studies reporting incidence rates.

The characteristics of the 11 studies reporting incidence data follows. Correa 2005 reported five participants with adverse events in the treatment group. These adverse events were related to the tolerability of a baby formula supplemented with probiotics. Dharani 2017 reported five adverse events in the treatment and nine adverse events in the control group, including flatulence, abdominal discomfort and vomiting. Fox 2015 reported 14 participants with adverse events (i.e. abdominal pain, loss of appetite, nausea, vomiting and headache) with more adverse events reported in the control group than the probiotic group. Kodadad 2013 reported 18 participants with adverse events

including nausea, vomiting, and abdominal bloating, again with more adverse events occurring in the control group than the probiotic group. Kolodziej 2018 reported three adverse events in probiotic group and seven adverse events in control group. In both groups adverse events included abdominal pain, regurgitation and 'flexing'. Merenstein 2009 reported a case of emesis in the treatment group and a case of constipation in the control group. Sykora 2005 reported seven adverse events in the probiotic group and nine adverse events in the control group. However, eight of the reported adverse events were diarrhea (four in each group) which we counted as our primary outcome. This left four participants with non-diarrhea adverse events in each group. No difference in adverse events was found between groups (P < 0.0001). Olek 2017 reported 155 adverse events in 99/447 participants randomized, of which 39 participants in treatment group and 60 participants in control group experienced at least 1 adverse event. The incidence of participants with at least one adverse event was significantly lower in the treatment group compared with the placebo-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. Peng 2014 reported adverse events including antibiotic allergic reaction and mycotic stomatitis. However, it was assumed for the purpose of our meta-analysis that the antibiotic allergic reaction was not related to the probiotics. Therefore, three adverse events were found in the control group and zero adverse events were found in the treatment group. Tankanow 1990 reported 14 adverse events experienced by 3 patients 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. Based on the study report, it appears that the 14 adverse events occurred in 3 participants receiving probiotic.

The characteristics of the one trial reporting a rate ratio are as follows. Among 240 patients randomized, Zhao 2014 reported 95/120 adverse events in treatment group and 140/120 adverse events in control group. The adverse events including nausea, vomiting, stomatitis, abdominal pain and constipation. However, the author did not report evidence of association between observed adverse events and probiotic. We contacted the author for the number of patients with at least one or more adverse events in each group (treatment and control) and no response was received.

Meta-analysis of 24 trials (4415 participants) that followed participants for adverse events demonstrated no differences in the incidence of adverse events. After 5 days to 4 weeks of follow-up, 4% (86/2229) of participants in probiotic group had adverse events compared to 6% (121/2186) of participants in control group (RD 0.00; 95% CI -0.01 to 0.01, P < 0.00001), demonstrating that there were slightly more adverse events in the control group. A GRADE analysis indicated that the overall quality of evidence for this outcome was low due to imprecision (sparse data, only 207 events), indirectness related to intervention and measurement of adverse outcomes, inconsistency (I^2 = 75%) and potential selective reporting given that only 25 of 33 studies reported AEs (see Summary of findings for the main comparison).

Mean duration of diarrhea

Eight studies recorded the mean duration of diarrhea (Arvola 1999; Correa 2005; Destura unpublished; Esposito 2017; LaRosa 2003; Peng 2014; Vanderhoof 1999; Zhang 2015). The standard deviation (SD) for two of the eight trials was not reported (Esposito 2017; Vanderhoof 1999). The SD of the two trials (Esposito 2017; Vanderhoof 1999), was imputed based on median of observed SD values from other 6 trials (Arvola 1999; Correa 2005; Destura unpublished; LaRosa 2003; Peng 2014; Zhang 2015). A post hoc sensitivity analysis was conducted to test the robustness of the mean duration results both before and after imputing data. The MD was statistically significant both before including Vanderhoof 1999 (MD -0.80; 95% CI -1.42 to -0.18; 1015 participants) and after imputing the SD data (MD -0.91, 95% -1.38 to -0.44; 1263 participants). Substantial heterogeneity was detected (P < 0.00001) and this was high with respect to per cent variability due to between (or inter -) study variability (I^2 = 84%, P < 0.00001) (Higgins 2003). A GRADE analysis indicated that the overall quality of evidence for this outcome was low due to serious inconsistency (I^2 = 84%) and potential selective reporting bias given that only 8 of 33 trials reported on duration of diarrhea (see Summary of findings for the main comparison).

Microbiome characteristics

One study reported on metabolic activity of the gut microflora (i.e. fecal urease, beta-glucuronidase, beta-glucosidase) at baseline, three weeks, one month and three months (Arvola 1999), however, authors did not report changes between groups. Since the Arvola 1999 data are specific to enzymatic activity of the microflora, we did not consider this directly relevant to microbiome characteristics. A second study that assessed five probiotic species including *Lactobacilli*, *Lactococci*, *Bifidobacterium* (strain not specified) versus no treatment (antibiotic only) reported fecal microflora composition changes in microbiome at baseline, one day after discontinuation of antibiotic, and one month after discontinuation (Zakordonets 2016). Authors reported that probiotics may lead to differences between the probiotic and the antibiotic only group with respect to total E. coli, lactose (-) and *hemolytic* E. coli, and *Staphylloccus aureas* at one day after discontinuation of antibiotic (P<0.05). At one month, authors also reported probiotics may lead to slight differences in lactose (-) and *hemolytic E. coli*, *Staphylloccus aureas*, *Candida spp* and *Klebsiella pneumoniae* (P < 0.05). There were no differences in changes in *Lactobacillus spp* or *Bifidobacterium spp* (P < 0.05). No studies reported 16SrRNA or other microbiome analyses. GRADE analysis indicated that overall quality of evidence for this outcome was very low due to selective reporting, imprecision, and indirectness (outcome not of importance to patients).

A PRIORI SUBGROUPS

1. Inpatient versus outpatient

Twenty-three studies clearly delineated whether or not their populations were inpatient or outpatient. Eleven studies were conducted in an outpatient setting (Benhamou 1999; Conway 2007; Correa 2005; Dharani 2017; Fox 2015; Jindal 2017; Merenstein 2009; Olek 2017; Saneeyan 2011; Tankanow 1990; Vanderhoof 1999). Ten studies were conducted amongst inpatient populations (Esposito 2017; Georgieva 2015; Jirapinyo 2002; King 2010; Peng 2014; Shan 2013; Szajewska 2009; Wan 2017; Zakordonets 2016; Zheng 2012). Seven studies had mixed inpatients and outpatient populations (Arvola 1999; Destura unpublished; Kolodziej 2018; Kotowska 2005; Ruszczynski 2008; Szymanski 2008; Zhao 2014). Both outpatient studies and inpatient studies showed a statistically significant

effect. Seven per cent (54/750) of inpatients in the probiotic group had diarrhea compared to 24% (171/719) of inpatients in the control group (RR 0.34; 95% CI 0.26 to 0.45). Eight per cent (99/1273) of outpatients in the probiotic group had diarrhea compared to 17% (200/1207) of outpatients in the control group (RR 0.54; 95% CI 0.33 to 0.88); in both instances probiotics reduced diarrhea. A test for interaction between in and outpatient trials was not statistically significant (P = 0.21; I^2 = 57.7%).

2. Diagnosis

Twenty-nine studies reported on the participants' diagnoses which had necessitated the antibiotics. Dharani 2017 was limited to patients with impetigo. Esposito 2017 was limited to hypospadias. Six studies (n = 1064) were limited to respiratory infections (Arvola 1999; Merenstein 2009; LaRosa 2003; Kotowska 2005; Peng 2014; Zheng 2012), of which 16% (58/532) of patients diagnosed with respiratory infections in probiotic group had diarrhea compared to 26% (136/532) in control group (RR 0.44; 95% CI 0.33 to 0.61; P < 0.00001). Six studies (n = 700) were limited to participants with *H. pylori* infections (Kodadad 2013; Saneeyan 2011; Sykora 2005; Szajewska 2009; Zhang 2015; Zhao 2014), of which 14% (49/353) of patients diagnosed with *H. pylori* infection in probiotic group had diarrhea compared to 30% (105/347) in control group (RR 0.48; 95% CI 0.35 to 0.64; P < 0.00001). Fifteen studies (n = 3083) had participants with a variety of infections (Destura unpublished; Fox 2015; Georgieva 2015; Jindal 2017; Jirapinyo 2002; King 2010; Kolodziej 2018; Olek 2017; Ruszczynski 2008; Shan 2013; Szymanski 2008; Tankanow 1990; Vanderhoof 1999; Wan 2017; Zakordonets 2016), of which 6% (89/1542) of patients in probiotic group had diarrhea compared to 17% (258/1541) in control group (RR 0.43; 95% CI 0.27 to 0.67; P <0.0001). A test for interaction was not statistically significant (P = 0.91; I^2 = 0%).

3. Probiotic species

Six of 33 trials administered *Lactobacillus rhamnosus* species (five using strain *Lactobacillus GG*: Arvola 1999; Esposito 2017; King 2010; Szajewska 2009; Vanderhoof 1999; and one using strains E/N, Oxy, and Pen: Ruszczynski 2008), while nine studied the yeast *Saccharomyces boulardii* (Benhamou 1999; Erdeve 2004; Jindal 2017; Kotowska 2005; Peng 2014; Shan 2013; Wan 2017; Zhang 2015; Zhao 2014). Combined results from six *L. rhamnosus* studies (n = 686) showed a statistically significant protective effect. Eight per cent (27/345) of *L. rhamnosus* participants had diarrhea compared to 22% (76/341) of the control group, (RR 0.37, 95% CI 0.24 to 0.55; P < 0.0001; I^2 = 0%). The summary statistic for *Saccharomyces boulardii* trials (n = 3165) was statistically significant as well indicating a protective effect. Eight per cent (125/1620) of *Saccharomyces boulardii* participants had diarrhea compared to 21% (329/1545) in control group (RR 0.36; 95% CI 0.24 to 0.54; P <0.0001; I^2 = 76%). A test of interaction for species related heterogeneity between *L. rhamnosus* species and *S. boulardii* revealed no statistically significant difference (P = 0.94, I^2 = 0%).

4. Single strain versus multi-strain probiotics

Of the 33 studies reporting on incidence of diarrhea, 20 studies used a single strain (Arvola 1999; Benhamou 1999; Destura unpublished; Erdeve 2004; Esposito 2017; Georgieva 2015; Jindal 2017; King 2010; Kolodziej 2018; Kotowska 2005; LaRosa 2003; Olek 2017; Peng 2014; Shan 2013; Sykora 2005; Szajewska 2009; Vanderhoof 1999; Wan 2017; Zhang 2015; Zhao 2014), four studies used two strains (Correa 2005; Jirapinyo 2002; Tankanow 1990; Zheng 2012), three studies used three strains (Fox 2015; Ruszczynski 2008; Szymanski 2008), three studies used four strains (Conway 2007; Dharani 2017; Zakordonets 2016), two studies used seven strains (Kodadad 2013; Saneeyan 2011), and one study used 10 strains (Merenstein 2009). Single strain probiotics (20 studies, n = 4900) and multi-strain probiotics (13 studies, n = 1452) showed a statistically significant effect. Seven per cent (184/2483) of single strain participants had diarrhea compared to 18% (446/2417) of the control group (RR 0.42, 95% CI 0.32 to 0.56; P < 0.00001). Ten per cent (75/749) of multi-strain participants had diarrhea compared to 22% (152/703) of the control group (RR 0.53; 95% CI 0.37 to 0.75; P = 0.0003). A test for interaction between these two groups was not statistically significant (P = 0.34; I^2 = 0%).

5. Probiotic dose

The daily dosage of probiotic(s) varied greatly from 100 million to 2 trillion CFUs/day. Thirty-two of 33 studies that reported on the incidence of diarrhea, provided dosage information (Arvola 1999; Benhamou 1999; Conway 2007; Correa 2005; Destura unpublished; Erdeve 2004; Esposito 2017; Fox 2015; Georgieva 2015; Jindal 2017; Jirapinyo 2002; King 2010; Kodadad 2013; Kolodziej 2018; Kotowska 2005; LaRosa 2003; Merenstein 2009; Olek 2017; Peng 2014; Ruszczynski 2008; Saneeyan 2011; Shan 2013; Sykora 2005; Szajewska 2009; Szymanski 2008; Tankanow 1990; Vanderhoof 1999; Wan 2017; Zakordonets 2016; Zhang 2015; Zhao 2014; Zheng 2012). The a priori subgroup analyses on dose compared < 5 billion CFUs/day versus ≥ 5 billion CFUs/day. Twenty studies (n = 4038) providing children with 5 billion to 2 trillion bacteria/yeast cells per day showed evidence for the preventative effects of probiotics (Arvola 1999; Erdeve 2004; Esposito 2017; Fox 2015; Jindal 2017; Kotowska 2005; LaRosa 2003; Merenstein 2009; Olek 2017; Peng 2014; Ruszczynski 2008; Shan 2013; Sykora 2005; Vanderhoof 1999; Wan 2017; Zakordonets 2016; Zhang 2015; Zhao 2014). For the high dose studies, the pooled incidence of AAD in the probiotic group was 8% (162/2029) compared to 23% (462/2009) in the active, placebo or no treatment control group (RR 0.37, 95% CI 0.30 to 0.46, P < 0.00001, I^2 = 36%, moderate certainty evidence; See Summary of findings for the main comparison). Twelve studies (n = 2214) providing < 5 billion CFUs bacteria/yeast per day: 825 million CFUs/day (Correa 2005), 200 million CFUs/day (Kolodziej 2018; Szymanski 2008), 100 million CFUs/day (Georgieva 2015), 4.5 billion CFUs/day (Benhamou 1999), 4 billion CFUs/day (Destura unpublished), 2.2 billion CFUs/day (Zheng 2012), 2 billion CFUs/day (Tankanow 1990), and 1 billion CFUs/day (Conway 2007; Szajewska 2009; Saneeyan 2011; Kodadad 2013), and demonstrated statistically non-significant results when combined. For the low dose studies the pooled incidence of AAD in the probiotic group was 8% (97/1155) compared to 13% (133/1059) in the active, placebo or no treatment control group (RR 0.68; 95% CI 0.46 to 1.01; P = 0.06; I^2 = 53%). A test for interaction revealed a statistically significant dose-related heterogeneity (P = 0.01; I^2 = 85.1%). Using 5 criteria to evaluate the credibility of the subgroup analysis, the results indicate that the subgroup effect based on dose (≥ 5 billion CFUs/day) was convincing (Sun 2014; See Appendix 2).

6. Definition of diarrhea

Among the 27 studies reporting on the definition of diarrhea onset (diagnosis), we assessed for subgroup differences based on the variability of the definition. Among studies (13 studies, n = 1873) defining diarrhea as 3 or more loose/water/liquid stools per day

for at least 2 consecutive days, 6% (58/956) of the probiotic group had diarrhea compared to 19% (170/917) of the control group (RR 0.36, 95% CI 0.25 to 0.50; P < 0.00001; I^2 = 15%). Among studies (9 studies, n = 2748) defining diarrhea as ≥ 3 watery/liquid stools per 24 hours, 8% (106/1408) of the probiotic group had diarrhea compared to 17% (228/1340) of the control group (RR 0.48, 95% CI 0.31 to 0.76; P = 0.0002; I^2 = 73%). A test for interaction by diarrhea definition was not statistically significant (P = 0.30, I^2 = 7%).

7. Strictness of definition of diarrhea (mild vs moderate)

Similarly, we assessed for subgroup differences based on categorizing the study definition of AAD as either mild or moderate severity. Among studies (20 studies, n = 4303) defining diarrhea as moderate severity, 7% (148/2207) of the probiotic group had diarrhea compared to 17% (365/2097) of the control group (RR 0.40, 95% CI 0.31 to 0.53; P < 0.00001; I^2 = 46%). Among studies (5 studies, n = 1104) defining diarrhea as mild severity, 9% (51/562) in probiotic group had diarrhea compared to 25% (134/542) in control group (RR 0.41, 95% CI 0.22 to 0.77; P = 0.005, I^2 = 81%). A test for interaction by strictness was not statistically significant (P = 0.95, I^2 = 0%).

8. Industry sponsorship

Seventeen studies clearly reported on study sponsorship or funding. Of these, 9 studies (n = 1627) were funded by industry (Correa 2005; Destura unpublished; Merenstein 2009; Olek 2017; Ruszczynski 2008; Sykora 2005; Tankanow 1990; Vanderhoof 1999; Zakordonets 2016) and 8 (n = 1315) were not (Conway 2007; Dharani 2017; Fox 2015; Jindal 2017; Kolodziej 2018; Saneeyan 2011; Szajewska 2009; Szymanski 2008). Industry sponsored studies showed statistically significant effects as did non-industry sponsored studies. Among industry sponsored studies, 8% (62/804) of the probiotic group had diarrhea compared to 15% (126/823) of the control group (RR 0.58, 95% CI 0.40 to 0.82; P = 0.003; I^2 = 39%). Among non-industry sponsored studies 6% (44/680) of the probiotic group had diarrhea compared to 18% (112/635) in control group (RR 0.43; 95% CI 0.18 to 1.00; P = 0.05, I^2 = 70%). A test for interaction between these two groups was not statistically significant (P = 0.52, I^2 = 0%).

9. Risk of bias

Of the 33 studies reporting on incidence of diarrhea, 13 studies (n = 2170) were rated as having a low risk of bias (Destura unpublished; Fox 2015; Georgieva 2015; Kodadad 2013; Kolodziej 2018; Kotowska 2005; LaRosa 2003; Merenstein 2009; Olek 2017; Ruszczynski 2008; Sykora 2005; Szajewska 2009; Szymanski 2008), and 20 studies (n = 4182) were rated as having a high risk of bias (Arvola 1999; Benhamou 1999; Conway 2007; Correa 2005; Dharani 2017; Erdeve 2004; Esposito 2017; Jindal 2017; Jirapinyo 2002; King 2010; Peng 2014; Saneeyan 2011; Shan 2013; Tankanow 1990; Vanderhoof 1999; Wan 2017; Zakordonets 2016; Zhang 2015; Zhao 2014; 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 of bias studies and the high risk of bias studies. Among low risk of bias studies, 7% (70/1076) of the probiotic group had diarrhea versus 13% (139/1094) of the control group (RR 0.53; 95% CI 0.37 to 0.77; P = 0.0007, I^2 = 32%). Among high risk of bias studies 9% (189/2158) of the probiotic group had diarrhea compared to 23% (459/2024) of the control group (RR 0.42; 95% CI 0.31 to 0.56; P < 0.00001, I^2 = 66%). A test for interaction was not statistically significant (P = 0.30; I^2 = 8.7%).

POST HOC SUBGROUPS

Age ≤24 months versus > 24 months

Thirty-two (n = 5752) of 33 studies reported on age. Based on the largest prospective cohort study we are aware of (Turck 2003), the risk of AAD based 650 outpatient children prescribed antibiotics is 18% in children ≤ 24 months, and 3% in children > 24 months. We assessed for subgroup difference based on these age groups. Of these, six studies (n = 1127) reported on the participants' age ≤ 24 months (Correa 2005; Esposito 2017; Jirapinyo 2002; Peng 2014; Wan 2017; Zheng 2012), while 26 studies (n=4625) enrolled participants > 24 months of age (Arvola 1999; Benhamou 1999; Conway 2007; Destura unpublished; Dharani 2017; Erdeve 2004; Fox 2015; Georgieva 2015; King 2010; Kodadad 2013; Kolodziej 2018; Kotowska 2005; LaRosa 2003; Merenstein 2009; Olek 2017; Ruszczynski 2008; Saneeyan 2011; Shan 2013; Sykora 2005; Szajewska 2009; Szymanski 2008; Tankanow 1990; Vanderhoof 1999; Zakordonets 2016; Zhang 2015; Zhao 2014). For the participants ≤ 24 months of age the pooled incidence of AAD in the probiotic group was 9% (50/580) compared to 25% (136/547) in the active, placebo or no treatment control group (RR 0.37; 95% CI 0.26 to 0.53; P = 0.24; I^2 = 26%). For those participants > 24 months of age the pooled incidence of AAD in the probiotic group was 8% (193/2354) compared to 17% (390/2271) in the active, placebo or no treatment control group (RR 0.50; 95% CI 0.39 to 0.66; P = 0.0006; I^2 = 54%). A test for interaction was not statistically significant (P = 0. 18; I^2 = 43.3%).

SENSITIVITY ANALYSES

Random-effects versus fixed-effect

A sensitivity analysis using random-effects (RR 0.45; 95% CI 0.36 to 0.56; P < 0.00001; I^2 = 57%) versus fixed-effect models (RR 0.43; 95% CI 0.37 to 0.49; P <0.00001, I^2 = 57%) 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 outcome data analysis

Incidence of diarrhea analysis

There were 6352 pediatric participants originally randomized in the 33 trials reporting on the primary outcome (incidence of diarrhea). Twenty of 33 trials reported LTFU of which six reported substantial attrition concerns. Loss to follow-up was 20%, 21%, 28%, 28%, 36% and 46.4% in the Szajewska 2009; Arvola 1999; Benhamou 1999; Erdeve 2004; Tankanow 1990 and King 2010 studies respectively. We elected to make assumptions about the missing data which were extreme but still plausible. If no information was reported 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 (e.g. 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 probable slight

reduction in the incidence of AAD. For this sensitivity analysis, the pooled incidence of AAD in the probiotic group was 12% (436/3551) compared to 19% (664/3468) in the active, placebo or no treatment control group (RR 0.61; 95% CI 0.49 to 0.77; P <0.00001; I^2 = 70%). For high dose probiotics, the extreme plausible analysis for LTFU also showed that the probiotics probably reduce the incidence of AAD (RR 0.54; 95% CI 0.42 to 0.70; P <0.00001; I^2 = 68%).

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 24 trials that did report on adverse events, the proportion of adverse events was 3.9% (86/2229) in the treatment group and 121/2186 (5.5%) 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, that is 3.8% (88/2331) and 5.4% (123/2264) were assumed to have adverse events among treatment and control groups, respectively.

Our primary complete case analysis (RD -0.00; 95% CI -0.01 to 0.01; P < 0.00001) yielded the same pooled estimate as the same event rate assumptions analysis (RD 0.00; 95% CI -0.01 to 0.01; P < 0.00001).

Publication bias

A funnel plot analysis provided no compelling visual 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

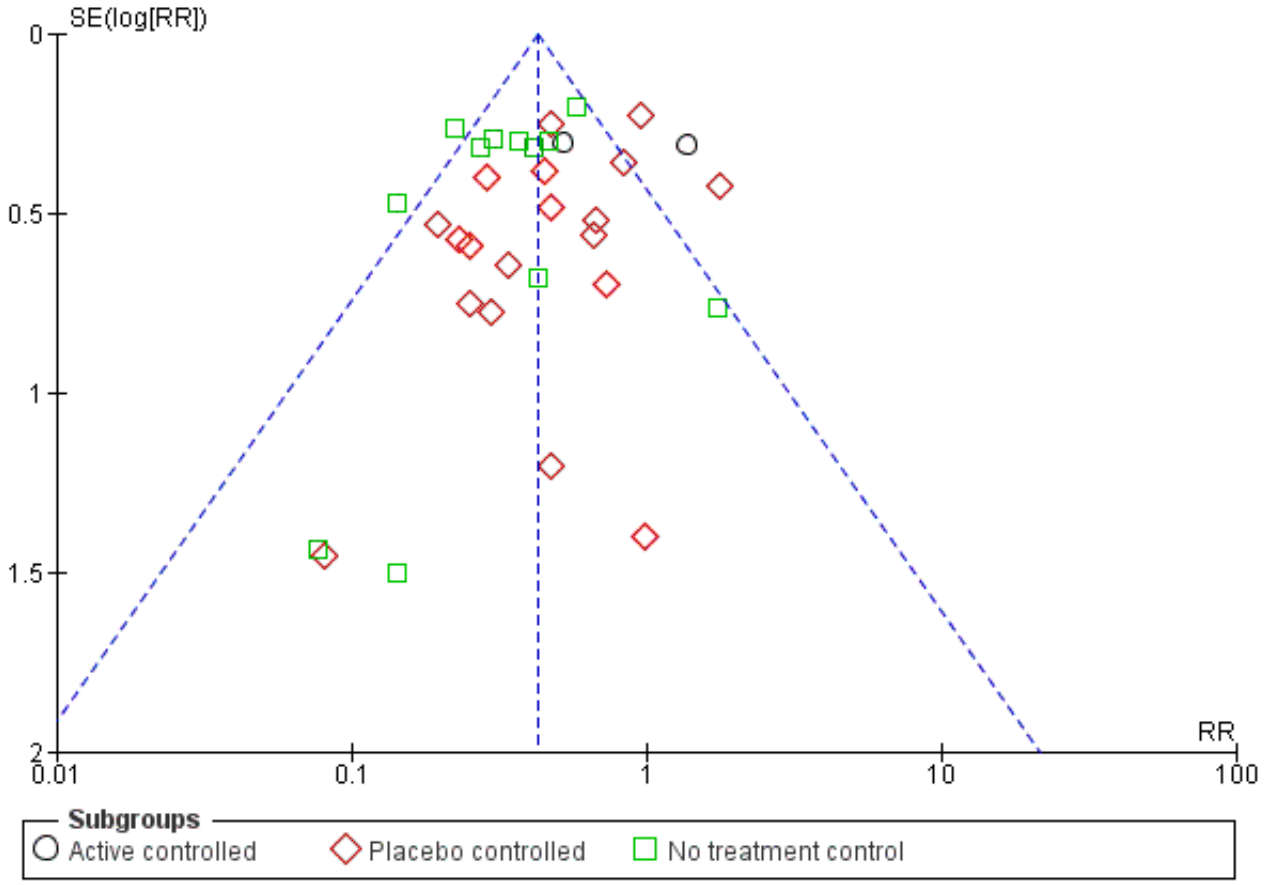
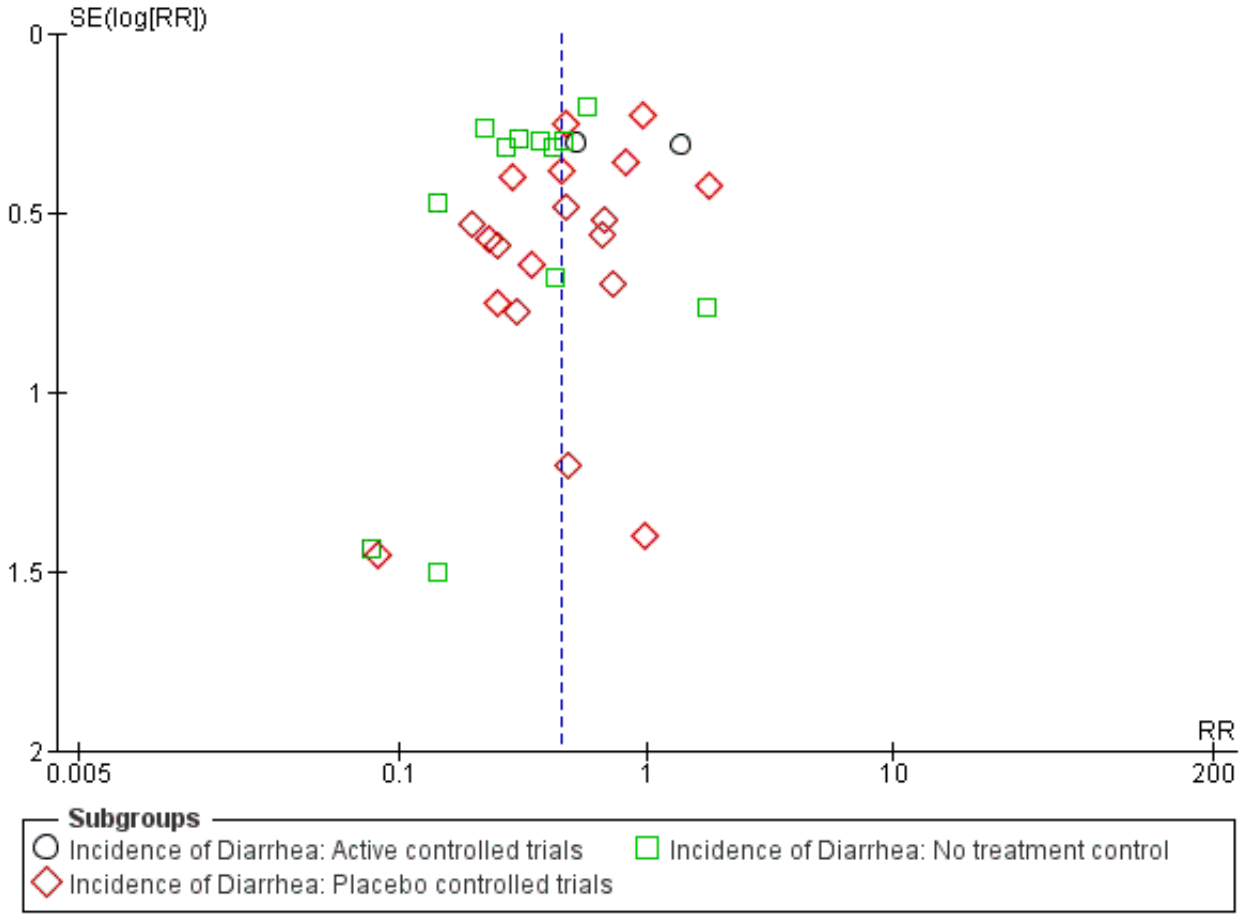


Figure 5. Funnel plot of comparison: 1 Probiotics versus control, outcome: 1.1 Incidence of diarrhea: Complete case.

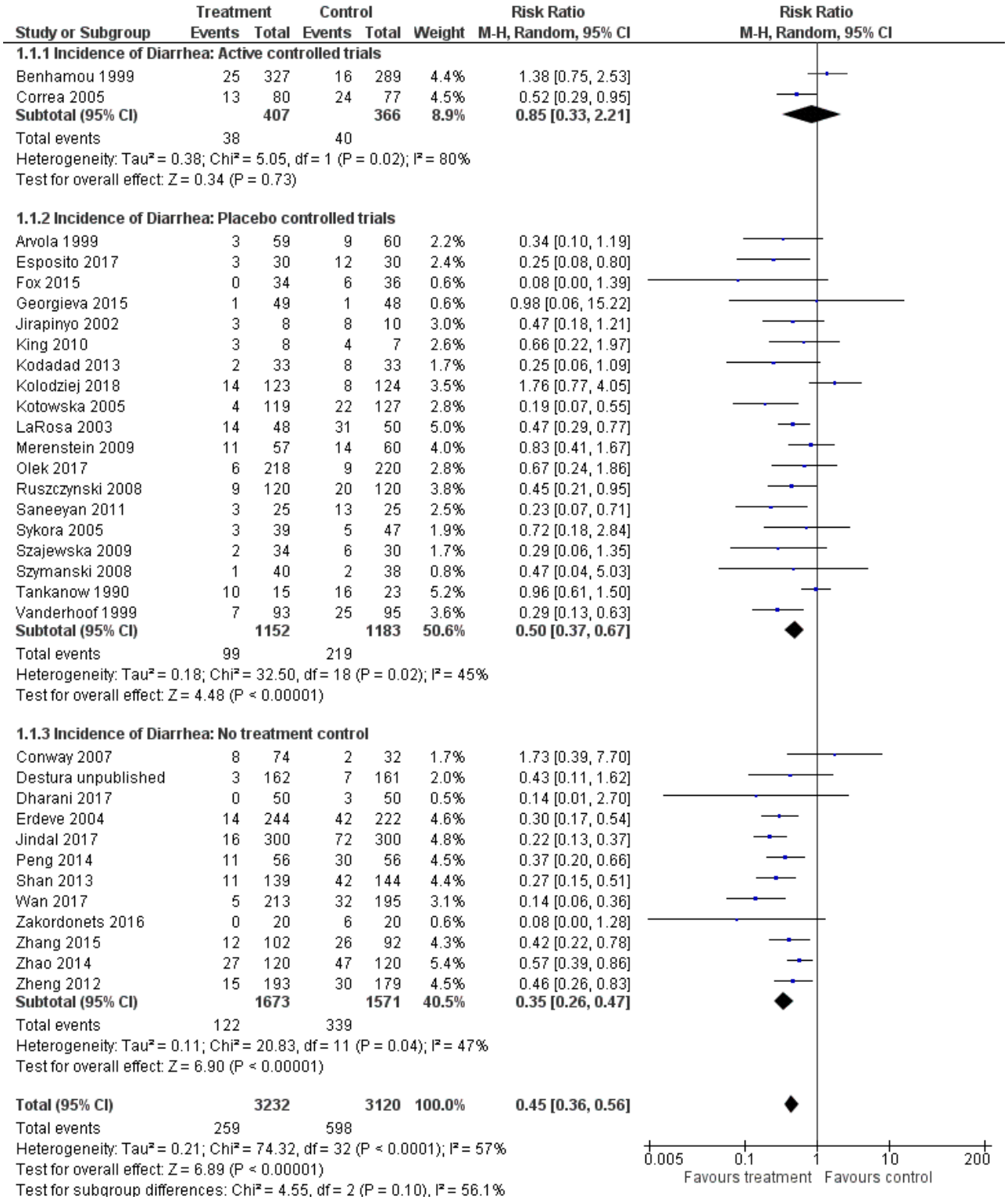


DISCUSSION

Summary of main results

The primary objective of this review was to determine if the co-administration of probiotics with antibiotics prevents the incidence of antibiotic-associated diarrhea in children. Thirty-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. Fifteen of 33 trials tested *S. boulardii* or *Lactobacillus rhamnosus spp*. Complete case analysis (i.e. patients who did not complete the studies were not included in the analysis) results from 33 trials reporting on the incidence of diarrhea, demonstrated a precise benefit with an incidence of AAD of 8% (259/3232) in the probiotic group compared to 19% (598/3120) in the control group (RR 0.45, 95% CI 0.36 to 0.56, P < 0.00001, I^2 = 57%; Figure 6). The NNTB to prevent one case of diarrhea is nine (NNTB 9; 95% CI 7 to 13), a moderate treatment effect.

Figure 6. Forest plot of comparison: 1 Probiotics versus control, outcome: 1.1 Incidence of diarrhea: Complete case.



To test the robustness of our complete case analysis, we elected to make assumptions about the missing outcome data which were extreme but arguably plausible. Nineteen of 33 trials had loss to follow-up ranging from 1.2% to 46.4%. 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 probable benefit for probiotics (7019 participants, RR 0.61, 95% CI 0.49 to 0.77, P < 0.0001; I^2 = 70%).

Statistical heterogeneity was moderate. We specified nine a priori subgroup hypotheses to explore the heterogeneity in our results,

including inpatient versus outpatient, diagnosis type, probiotic species or strain, single versus multi strain, probiotic dose, definition of diarrhea, strictness of definition (mild versus moderate severity), industry sponsorship, and risk of bias (e.g. allocation concealment, blinding). We also conducted a post hoc subgroup analysis which included age (≤ 24 months versus > 24 months). A test for heterogeneity was significant for one subgroup: probiotic dose, providing evidence that a dose-response gradient is the most likely explanation for the statistical heterogeneity. The test for interaction for potential dose-associated heterogeneity was statistically significant (P = 0.01). Using 5 criteria to evaluate the credibility of the subgroup analysis, the results indicate that the subgroup effect based on dose (≥ 5 billion CFUs per day) was convincing (Sun 2014); see Appendix 2). This represents an important finding as dosage recommendations for products containing probiotics available in pharmacies and health food stores have a wide range (e.g. 0.2 billion to 2 trillion CFUs per day). Dosages approaching the lower range may not confer a benefit (Ouwehand 2017; Raza 1995), while doses in the upper range may be associated with an increased risk of adverse events. Given our review included trials testing 19 different probiotics (single or multi-agent species), amongst a diverse clinical population, with nearly all demonstrating favourable results; for the purposes of clinical use and future research, our findings suggest that the minimal effective dose may be 5 billion CFUs per day, with an upper range of 40 billion CFUs/day considered efficacious in otherwise healthy children (RR 0.37, 95% CI 0.30 to 0.46; NNTB 6, 95% CI 5 to 9). Further, although we did not observe a statistically significant effect based on our post-hoc subgroup on age, evidence from the largest cohort study we are aware of assessing the risk for AAD among 650 outpatient children in France suggests a six-fold increased risk of AAD in children ≤2 years of age (18% risk of AAD) versus children > 2 years (3% risk of AAD) of age (Turck 2003). Based on the RR from trials administering ≥5 billion CFUs/day, for children ≤2 years of age the absolute risk reduction is 113 fewer AAD cases per 1000 children followed (95% CI 97 to 126 fewer cases), while for children > 2 years of age the absolute risk reduction is 19 fewer AAD cases per 1000 children followed (95% CI 16 to 21 fewer cases). These results, although post-hoc, suggest that probiotics are substantially more effective in younger children.

Regarding safety, 24/33 trials reported on adverse events, none having reported a serious adverse event. Meta-analysis demonstrated no substantial differences in the incidence of any adverse events between treatment and control (RD 0.00, 95% CI -0.01 to 0.01, P < 0.59; I^2 = 75%).

Overall completeness and applicability of evidence

We included 33 trials of children (n=6352), both male and female aged from 3 days to 18 years (6 studies in those ≤2 years, 26 studies in those >2 years) from diverse socioeconomic status across 17 countries including both developed country and developing countries. We believe the population is varied enough for results to be generalized to healthy children receiving antibiotics. However, only one study included newborns and one study with just 15 participants was conducted in the Intensive Care Unit (ICU), thus the applicability of our results to newborns and ICU children is unknown.

Studies used 19 different probiotic interventions including different species and/or strain(s), as well as dosages versus placebo (19 studies), no probiotics (12 studies) and active control (2 studies). We did subgroup analysis to explore the different interventions, both species and strain and the results demonstrated no difference in the prevention of AAD, suggesting enhanced generalizability of our findings. For the dosage of probiotics, a test for interaction revealed that the subgroup effect based on high dose (≥ 5 billion CFUs/day) probiotics was superior to low dose, suggesting that high dose interventions of various probiotics are most likely to be beneficial (particularly Lactobacillus GG and Saccharomyces boulardii, the most studied products).

The outcome, incidence of AAD, was reported in all included studies, while 24 studies (n = 4415) reported on the potential for adverse events. However, our findings are not representative of all available data on adverse events as we only included randomized trials, whereas observational studies may suggest the potential for harm in some pediatric populations. With respect to secondary outcomes, only 9 studies reported on duration of diarrhea (n=1263) and one study reported the microbiome characteristics. Although the results of microbiome characteristics are generally unaddressed and may be helpful to understanding the probiotic mechanism of action, we believe the data on AAD and adverse event outcomes directly answer the question that clinicians and researchers have.

Quality of the evidence

Using the Cochrane risk of bias tool, we rated 13 trials as low risk of bias (Destura unpublished; Fox 2015; Georgieva 2015; Kodadad 2013; Kolodziej 2018; Kotowska 2005; LaRosa 2003; Merenstein 2009; Olek 2017; Ruszczynski 2008; Sykora 2005; Szajewska 2009; Szymanski 2008). Twenty trials were rated as high risk of bias (Arvola 1999; Benhamou 1999; Conway 2007; Correa 2005; Dharani 2017; Erdeve 2004; Esposito 2017; Jindal 2017; Jirapinyo 2002; King 2010; Peng 2014; Saneeyan 2011; Shan 2013; Tankanow 1990; Vanderhoof 1999; Wan 2017; Zakordonets 2016; Zhang 2015; Zhao 2014; Zheng 2012). The most common reasons for a high risk of bias rating were lack of blinding and incomplete outcome data.

The certainty of evidence supporting each outcome was determined using the GRADE criteria (Guyatt 2008). For the main efficacy outcome, incidence of diarrhea, the certainty of the evidence was rated 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 the minor issues with risk of bias related to poor reporting regarding allocation concealment, blinding and incomplete data, as well as inconsistency related to the diversity of probiotics used. For the incidence of adverse events the certainty of the evidence was rated as low (we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the effect estimate). 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 (eight trials, n = 1263), using a complete case analysis, probiotics decreased the mean duration of diarrhea by almost one day (MD -0.91; 95% CI -1.38 to -0.44), representing a moderate treatment effect. The certainty of the evidence was rated 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 varied 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 systematic review of the methods used in RCTs evaluating 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 8 of 33 trials assessing probiotics for the prevention of pediatric AAD reported on duration of diarrhea as a primary or secondary outcome.

With respect to microbiome characteristics, only one study reported such an analysis. Zakordonets 2016 used five probiotic species including *Lactobacilli*, *Lactococci*, *Bifidobacterium* (strain not specified) versus no treatment (antibiotic only) and reported on fecal microflora composition changes in microbiome at baseline, one day after discontinuation of antibiotic, and one month after discontinuation of antibiotic. The authors reported slight differences between the probiotic and the antibiotic only group with respect to total E. coli, lactose (-) and *hemolytic* E. coli, and *Staphylloccus aureas* at one day after discontinuation of antibiotic ($P < 0.05$). At one month, Zakordonets 2016 also reported slight differences in lactose (-) and *Hemolytic* E. coli, *Staphylloccus aureas*, *Candida spp* and *Klebsiella pneumoniae* ($P < 0.05$). There were no changes in *Lactobacillus spp* or *Bifidobacterium spp* ($P < 0.05$). No studies reported on 16S rRNA or other microbiome analyses. GRADE analysis indicated that overall quality of evidence for this outcome was very low due to selective reporting, imprecision, and indirectness (outcome not of importance to patients).

Potential biases in the review process

This systematic review has several strengths. We asked a clear and relevant clinical question and the search strategy for this review was comprehensive including all relevant trials irrespective of language or publication status (i.e. we included unpublished data from Destura unpublished and abstract data from King 2010; and we obtained pediatric specific data from Conway 2007). Additional strengths of the review include the independent application of the GRADE criteria to assess the certainty of evidence for each of the outcomes (Guyatt 2008), and the rigorous evaluation of nine a priori subgroups (e.g. inpatient versus outpatient, diagnosis type, probiotic species, single versus multi strain, probiotic dose, definition of diarrhea, strictness of definition (mild versus moderate), industry sponsorship, and risk of bias) using the five criteria for assessing subgroup credibility (Sun 2014).

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 *a priori* subgroup analyses and found no statistically significant differences between species or strains. Third, only one study assessed changes in microbiome characteristics before and after antibiotic and probiotic administration demonstrating no important differences. However, our findings are not representative of all available data on the topic as we only included randomized trials that assessed AAD as an outcome. For instance, a recent non-randomized controlled trial examined the potential effects of an 11 strain probiotic versus fecal transplantation versus no treatment on the microbiome after broad-spectrum antibiotic use in 21 healthy adults (Suez 2018). Probiotics were associated with a delay in transcriptome reconstitution of indigenous stool and mucosal microbiome configuration, while transplantation was associated with a quick and complete recovery after just a few days. Although Suez 2018 did not examine concurrent use of probiotics with antibiotics, nor did they examine children, their findings raise questions about the use of probiotics after antibiotic use. Unfortunately, there are many examples of early findings from laboratory experiments such as this with apparent harmful or salutary physiological effects, yet with subsequent clinical studies there is no apparent affect when assessing more patient-important outcomes (Ferreira 2007). Hence, focusing on the findings from Suez 2018 can only provide indirect low quality evidence for clinical outcomes of importance to patients such as diarrhea or quality of life (Johnston 2013).

Finally, our findings are based on an aggregate data meta-analysis and this does not allow us to fully explore participants (e.g. sex) and intervention level variables (e.g. number of antibiotics prescribed) that may be associated with AAD. To explore this issue in meta-analysis, one would require individual patient data which we do not currently have access to.

Agreements and disagreements with other studies or reviews

At least thirteen systematic reviews and 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). Six meta-analyses of randomized trials evaluating 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 0.52, 95% CI 0.38 to 0.72; Johnston 2011; RR 0.46; 95% CI 0.35 to 0.61; Goldenberg 2015; RR 0.43; 95% CI 0.33 to 0.56; McFarland 2015; RR 0.44; 95% CI 0.25 to 0.77; Szajewska 2006; RR 0.48; 95% CI 0.26 to 0.89; Szajewska 2015). This systematic review is an update of a previously published Cochrane review (Johnston 2007; Johnston 2011; Goldenberg 2015). This updated Cochrane review identified an additional 11 trials reporting on AAD, thus increasing the precision of our earlier results.

AUTHORS' CONCLUSIONS

Implications for practice

Moderate quality evidence suggests a protective effect of probiotics in preventing AAD. A test for heterogeneity indicates that a dose-response gradient explains the observed statistical heterogeneity. Using five criteria to evaluate the credibility of the subgroup analysis on probiotic dose, complete case results indicate that the subgroup effect based on dose (≥ 5 billion CFUs per day) was credible, demonstrating a large, precise benefit of high dose probiotics (RR 0.37; 95% CI 0.30, 0.46; P = 0.06; I^2 = 36%). Based on high-dose probiotics, the NNTB to prevent one case of diarrhea is six (NNTB 6; 95% CI 5 to 9). The likelihood of serious adverse events is very rare. The bulk of evidence exists for *Lactobacillus GG* and *Saccharomyces boulardii*. 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 mostly healthy children (noting that we included two small trials of children in the intensive care and neonatal unit), serious adverse events have been observed, mostly from case reports, in severely debilitated or immuno-compromised children with underlying risk factors including central venous catheter use and disorders associated with bacterial/fungal translocation.

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 minor issues with risk of bias and inconsistency (19 probiotic products used among 33 trials). Large trials are needed to better evaluate single or multiple strain specific probiotics among: 1) outpatients on oral antibiotics, 2) inpatients on intravenous antibiotics and 3) immune-compromised patients. In addition to assessing probiotics for the prevention of AAD, these trials should better assess the safety of probiotics and the potential impact of probiotics on the duration of diarrhea. In assessing safety, trials should define potential adverse events a priori and monitor for these adverse reactions according to available guidelines (Bafeta 2018; Ioannidis 2004).

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* 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

Arvola 1999 *(Continued)*

	Age: 2 weeks to 12.8 yrs (mean 4.5 yrs)
Interventions	Probiotics: *Lactobacillus GG* (4 billion CFUs/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)	Unclear risk	Without protocol and register information
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 CFUs/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

Benhamou 1999 *(Continued)*

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)	Unclear risk	Not reported. No protocol and registered
Other bias	Unclear risk	No funding from industry or other sources mentioned

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 CFUs 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

Conway 2007 *(Continued)*

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 yogurts. 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 un-blinded
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)	Unclear risk	Not reported. No protocol and register information
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 CFUs/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

Correa 2005 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind: The appearance and odour of the probiotic and non-supplemented 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*
Selective reporting (reporting bias)	Unclear risk	Not reported. No protocol and register information.
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 CFUs 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

Destura unpublished *(Continued)*

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.” “ 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 (NCT00447161) 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

Dharani 2017

Methods	A randomized, single blinded trial Withdrawals/Loss to follow-up: 0 ITT: N/A Period of follow-up: At the end of five days of treatment
Participants	N=100 Diagnosis: Patients with impetigo Country: India Setting: Outpatient departments Age: 1 to 15 years old
Interventions	Probiotics: *Lactobacillus* sporegens (50 million spores), *Streptococcus faecalis* (30 million spores), *Clostridium butyricum* (2 million spores) and *Bacillus mesentericus* (1 million spores) twice daily for 5 days Antibiotics: Azithromycin 10mg/kg/day for 5 days
Outcomes	ID: 0 in treatment (0/50), 3 in control (3/50) Definition of diarrhea: Not reported
Notes	Funding: Not reported

Risk of bias

Bias	Authors' judgement	Support for judgement

Dharani 2017 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	"A prospective randomized single blinded interventional study". However, the sequence generation process was not reported
Allocation concealment (selection bias)	Unclear risk	The method used to conceal allocation sequence was not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	The author described the study as single blinded. However, there is no information regarding who was blinded or how blinding was done . We assumed it was difficult to blind patients (or parents) and clinicians because the number of drugs used in the two groups of patients was different (azithromycin plus probiotic in treatment, azithromycin in control). Additionally, the timing of treatment was also different (probiotic 2 hours before meals, azithromycin 2 hours after meals)
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Unclear risk	There is no published protocol of this trial to assess reporting bias
Other bias	Unclear risk	The source of funding for was not reported. However, with regards to conflict of interest, the author "declared none"

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 CFUs/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

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

Erdeve 2004 *(Continued)*

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)	Unclear risk	Not reported. No protocol and register information
Other bias	Unclear risk	No mention of funding

Esposito 2017

Methods	A "prospective, randomized, placebo-controlled study" with 3 groups of patients Withdrawals/loss to follow-up: 0 (data provided by author) ITT: N/A Period of follow-up: At the end of hospitalization
Participants	N = 90 enrolled Diagnosis: Patients undergoing hypospadias repair Country: Italy Setting: Inpatient Age: 11 to 36 months
Interventions	Probiotic: *Lactobacillus rhamnosus* GG (ATCC53103) (5 billion CFUs/day) Antibiotics: amoxicillin+clavulanate ormacrolide
Outcomes	ID: treatment 3/30 (10%), placebo control 12/30 (40%), blank control 15/30 (50%) Definition of diarrhea: 3 or more liquid stools in a 24-hour period (Bristol stool chart, type 7)
Notes	Funding: not reported; no conflict of interest declared

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The randomization process was not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described. However, participants of the treatment group and the placebo control group may not have known whether they were receiving a probiotic or not (both were in the form of drops at the same time of day). It would have been difficult to blind the blank control group as they were receiving fewer medications
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study

Esposito 2017 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	There is no published protocol for assessing reporting bias
Other bias	Unclear risk	Source of funding not mentioned. However, they declared no conflict of interest

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 CFUs/day, Bb-12 5.9×10^9 CFUs/day, La-5 8.3×10^9 CFUs/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 ≥ 5 and stool frequency ≥ 2/day for more than 2 days; (B) stool consistency ≥ 5 and stool frequency ≥ 3/day for more than 2 days; (C) stool consistency ≥ 6 and stool frequency ≥ 2/day for more than 2 days; and (D) stool consistency ≥ 6 and stool frequency ≥ 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

Fox 2015 *(Continued)*

		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 2015

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: 97 participants were described the diagnosis.Infections of respiratory (n = 42) (43.3%), gastrointestinal, liver, pancreas infection (n = 23) (23.7%), eyes, nose, throat infection (n = 16) (16.5%), urinary tracts infections (8) (8.2), others (n = 8) (8.2%) Country: Bulgaria Setting: hospital admitted patients Age: 3-12 years mean 8.85 years
Interventions	Probiotics: 100 million CFUs per day *Lactobacillus reuteri* DSM 17938 Antibiotics: Amikacin (n = 1), Cefazoline (n = 38), Cefotaxime (n = 1), Ceftriaxon (n = 41), Cefuroxime (n = 4), Levofloxacin (n = 1), Metronidazol (n = 3), Piperacillin (n = 7)
Outcomes	ID: Control 1 (2.1%) versus Treatment 1 (2.04%) 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: The clinical trial has been supported by a grant from BioGaya AB, Sweden
Risk of bias	

Georgieva 2015 *(Continued)*

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 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 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	The outcomes of the full text is the same as a priori listed in clinicaltrials.gov (NCT01295918)
Other bias	High risk	The clinical trial has been supported by a grant from BioGaya AB, Sweden

Jindal 2017

Methods	A randomized, open, parallel group study Withdrawals/Loss to follow-up: 0 ITT: N/A Period of follow-up: 14 days after the start of an antibiotic
Participants	N = 600 Diagnosis: Tonsillitis, otitis, UTI Country: India Setting: Outpatient department of tertiary hospital Age: 6 months to 12 years
Interventions	Probiotics: *Saccharomyces boulardii*, 2-3 billion CFUs twice a day Antibiotics: Co-amoxyclav, Cefpodoxime, Cefdinir, Cefixime, Cephalexin
Outcomes	ID: 16 in treatment group (16/300, 5.3%), 72 in control group (72/300, 24%)

Jindal 2017 *(Continued)*

	Definition of diarrhea: 3 or more abnormally loose stools in 24 hours
Notes	Funding: Unfunded

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Mentioned randomization but otherwise not described: "Children were randomly divided into two groups"
Allocation concealment (selection bias)	Unclear risk	No information available regarding the method to conceal allocation sequence"
Blinding (performance bias and detection bias) All outcomes	High risk	Blinding was not done: "A randomized, open, parallel study was conducted"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study. 600 were eligible, and 600 completed the study
Selective reporting (reporting bias)	Unclear risk	There is no published protocol for assessing reporting bias
Other bias	Low risk	The study was funded by the author. There was no other declared conflict of interest

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 CFUs 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
Random sequence generation (selection bias)	Unclear risk	Based on a randomization list. Unclear how that was generated

Jirapinyo 2002 *(Continued)*

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

King 2010

Methods	Randomized, double-blind, placebo controlled trial Withdrawals/Loss to follow-up: 13/28 (46%) ITT: No Period of follow-up: not reported
Participants	N = 28 Diagnosis: Pneunonia, RSV, seizure, acute respiratory failure, cardiac arrest, meningitis, sepsis/bacteremia, altered mental status/water intoxication, neutropenia, renal failure Country: United States Setting: PICU (Pediatric Intensive Care Unit) Age: 21 days-11 years old
Interventions	Probiotics: *Lactobacillus GG*, 30 billion CFUs/day Antibiotics: Cephalosporins, clindamycin, vancomycin, other (not specified)
Outcomes	ID: 3 in treatment (3/8, 37.5%), 4 in control (4/7, 57.1%) Definitions of diarrhea: More than 3 loose stools in 24 hours
Notes	Funding: Not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified besides "randomization occurs a priori"

King 2010 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not detailed beyond "a patient identification number is assigned by pharmacy personnel"
Blinding (performance bias and detection bias) All outcomes	Low risk	The author reported that the study was "double-blinded, placebo-controlled" and noted that a "matching capsule" was used
Incomplete outcome data (attrition bias) All outcomes	High risk	Significant attrition: 13 participants either withdrew or were lost to follow-up
Selective reporting (reporting bias)	Unclear risk	At the time of review, this was an abstract only. There is no published protocol
Other bias	Unclear risk	Not reported but noted they had no disclosures

Kodadad 2013

Methods	Randomized, placebo-controlled study, double-blinded Withdrawals/Loss-to-follow-up: 0 (0%) ITT: Not reported 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 CFUs/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)
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

Kodadad 2013 *(Continued)*

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 (Iranian Registry of Clinical Trials: IRCT201201218793N1)
Other bias	Low risk	Based on registry info it is sponsored by the university of Tehran

Kolodziej 2018

Methods	Randomized, placebo-controlled study, triple-blind trial Withdrawals/Loss to follow-up: 2/125 in treatment group (1.6%), 1/125 in control group (0.8%) ITT: Yes Period of follow-up: 7 days after the end of antibiotics and probiotics/placebo
Participants	Children younger than 18 years who received antibiotic therapy within 24 hours of enrollment
Interventions	*Lactobacillus reuteri* DSM 17938
Outcomes	Incidence of diarrhea and AAD; frequencies of infectious diarrhea; need for discontinuation of antibiotic treatment; need for hospitalization to manage diarrhea (in outpatients); need for intravenous rehydration in any of the study groups;adverse events
Notes	The study was funded by the Medical University of Warsaw with study products being provided by Bio-Gaia

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"A computer-generated randomization list was prepared by a person unrelated to the trial"
Allocation concealment (selection bias)	Low risk	"Sequentially numbered, sealed, opaque envelopes containing the treatment assignment...were concealed from the enrolling physicians"
Blinding (performance bias and detection bias) All outcomes	Low risk	"All the investigators, caregivers, outcome assessors, and the person responsible for the statistical analysis remained blinded until the completion of the study"
Incomplete outcome data (attrition bias) All outcomes	Low risk	The number of participants lost to follow-up is low (1.2%, 3/250): 2 in treatment group and 1 in control group

Kolodziej 2018 *(Continued)*

Selective reporting (reporting bias)	Low risk	According to the protocol published in 2016, the author has reported all the results
Other bias	Low risk	The study was funded by the Medical University of Warsaw. The author has no conflict of interests

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 CFUs/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
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)	Unclear risk	Not reported. No protocol and register information
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
Interventions	Probiotic: LS (5.5 billion CFUs/day) with Prebiotic: FOS (250 mg/day) 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

Merenstein 2009 *(Continued)*

	Country: USA Setting: primary care office Age: 2.9 years treatment and 3.2 years control
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 CFUs 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 (NCT00481507)
Other bias	Low risk	Lifeway foods provided drink and funding although no author was associated with the company

Olek 2017

Methods	Randomized, double-blind, placebo-controlled, multicenter trial Withdrawal/Loss to follow-up: 9/447 (2%) ITT: N/A Period of follow-up: 14 days following end of antibiotic treatment
Participants	N = 447 Diagnosis: Respiratory tract infection (n = 217, 49.5%), throat infection (n = 149, 34%), ear infection (n = 57, 13%) and urinary tract infection (n = 11, 2.5%) Country: Poland Setting: Outpatient, 13 primary healthcare centers

Olek 2017 *(Continued)*

	Age: 1-11 years, mean 5.2±2.7 years
Interventions	Probiotics: *Lactobacillus plantarum* DSM 9843 (LP299V) 10 billion CFUs per day Antibiotics: Penicillins (n = 186), cephalosporins (n = 118), sulfamethoxazole and trimethoprim (n = 32), macrolides (n = 101)
Outcomes	ID: Treatment 85 (39%), control 98 (44.5%) Incidence of AAD: Treatment 6 (2.8%), control 9 (4.1%), Definition of diarrhea: At least 1 loose/watery stool (Bristol Stool Chart - Type 6-7) Definition of AAD: Three or more (≥3) loose/watery stools per day starting 2 hours after initiation of antibiotic treatment until the end of the study AE: In total, 155 adverse events in 99 children were reported by parents. Placebo vs LP299V: 27.3% vs 17.9%. No serious adverse events reported in the study.
Notes	Funding: The study was supported by Probi AB Solvegatan. I.A., N.L., and G.O. are employed by Probi AB. A.O. is managing director of CRO (MEDICAL NETWORK) contracted for conducting this study. M.W. and J.K. are co-owners of CRO (MEDICAL NETWORK) contracted for conducting this study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The randomization list used for the labelling and allocation of the study product was generated using SAS Proc v9.1." "1:1 randomization in blocks of 4"
Allocation concealment (selection bias)	Low risk	"The boxes containing LP299V/placebo were numbered, and the lowest available number at the study site was assigned by the investigator to a patient recruited into the study"
Blinding (performance bias and detection bias) All outcomes	Low risk	"The information about the allocation to specific study arm remained blind to patients, parents, and all members of the study team including the investigators monitors, and data managers who assessed the study outcomes until all data were collected and verified" "Placebo capsules had the same appearance, texture and taste as those with the active product"
Incomplete outcome data (attrition bias) All outcomes	Low risk	The number and reasons for those lost to follow-up (n=9) were described and comparable across groups AEs have been reported
Selective reporting (reporting bias)	Low risk	All outcomes have been reported based on the list on the clinical trials website (NCT01940913)
Other bias	High risk	The study ws supported by Probi AB Solvegatan. Three authors (I.A., N.L., and G.O.) are employed by Probi AB. A.O. is managing director of CRO (MEDICAL NETWORK) contracted for conducting this study. M.W. and J.K. are co-owners of CRO (MEDICAL NETWORK) contracted for conducting this study

Peng 2014

Methods	Randomized according the random number table method

Peng 2014 *(Continued)*

	Withdrawal/Loss to follow-up: 0 ITT: N/A Period of follow-up: Not provided
Participants	N = 112 Diagnosis: Newborns with pneumonia Country: China Setting: Inpatient Age: 3-28 days (mean 11.5±4.2 days)
Interventions	Probiotics: *Saccharomyces boulardii* 250mg (5 billion CFUs) per day, twice a day Antibiotics: Not reported
Outcomes	ID: Treatment 11 (19.6%), control 30 (53.6%) Definition of diarrhea: Increased bowel movements 72 hours after hospitalization to more than 3 times a day, and with a change in stool consistency
Notes	Funding: Not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The participants were divided into a treatment group and a control group according to a random number table
Allocation concealment (selection bias)	High risk	Not described. However, the probiotic group received 2 medications and control group received 1 medication thus we determined that allocation was not concealed
Blinding (performance bias and detection bias) All outcomes	High risk	Not described. Unlikely to have been blinded. The treatment group was given antibiotics and the control group was given antibiotics plus probiotics
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study. 112 neonates were included, and 112 were analyzed
Selective reporting (reporting bias)	Unclear risk	There is no published protocol to provide this information
Other bias	Unclear risk	The source of funding was not described The diagnosis of diarrhea in neonates is very difficult because their stool is usually loose or liquid and they have multiple bowel movements every day. Newborns with 7 or 8 loose stools per day may still be considered "normal"

Ruszczynski 2008

Methods	Randomized, placebo-controlled, double blind

Ruszczynski 2008 *(Continued)*

	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 CFUs 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)	Unclear risk	Not reported. No protocol and register information
Other bias	Low risk	Biomed provided the intervention but they “had no role in the conception, design, or conduct of the study or in the analysis or interpretation of the data"

Saneeyan 2011

Methods	Randomized, placebo-controlled, patient blinded

Saneeyan 2011 *(Continued)*

	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 CFUs 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
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

Shan 2013 *(Continued)*

	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 CFUs/day) Antibiotics: cefepime, cefoperazone, sulbactam, cefuroxime, amoxicillin, clavulanic acid, erythromycin
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)	Unclear risk	Not registered. No protocol
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

Sykora 2005 *(Continued)*

	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 CFUs/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
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)	Unclear risk	Not registered and no protocol published . 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

Szajewska 2009 *(Continued)*

	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 CFUs/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
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)	Unclear risk	Not registered. No protocol. 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)

Szymanski 2008 *(Continued)*

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 CFUs 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
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)	Unclear risk	Not reported. No protocol and registered information
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

Tankanow 1990 *(Continued)*

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 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)	Unclear risk	Not registered. No protocol. 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)

Vanderhoof 1999 *(Continued)*

Interventions	Probiotics: *L. GG* (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 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)	Unclear risk	Not reported. No protocol and register information
Other bias	Unclear risk	Lead author is a consultant for CAG nutrition (division of ConAgra) which makes the product

Wan 2017

Methods	Randomized study by means of random block allocation Withdrawal/loss to follow-up: None ITT: N/A Period of follow-up: 14 days after discontinuation of antibiotic therapy
Participants	N = 408

Wan 2017 *(Continued)*

	Diagnosis: Respiratory tract infection or pneumonia (n = 368); Pertussis (n = 6); Kawasaki Disease (n = 3); Urinary infection (n = 5); Scarlet fever (n = 1); Congenital syphilis (n = 1) Country: China Setting: Inpatient Age: 1 month-3 years (mean 1.14 years)
Interventions	Probiotics: *Saccharomyces boulardii* 250mg (5 billion CFUs) per day Antibiotics: 1 to 2 antibiotics, type not specified
Outcomes	ID: Treatment 5 (2.3%), control, 32 (16.4%) Definition of diarrhea: Increased stool frequency to at least twice a day, with change in stool consistency for more than 48 hours. Need to rule out rotavirus enteritis, bacterial dysentery and gastrointestinal infections such as food poisoning, and diarrhea caused by non-infectious causes such as inflammatory bowel disease and irritable bowel syndrome
Notes	Funding: Not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Children were randomly divided into control and prevention group by means of block random allocation method"
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding (performance bias and detection bias) All outcomes	High risk	Not described. Unlikely to be blinded. The treatment group was given antibiotic plus probiotic and the control group was given antibiotic and symptom-associated treatment
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up: 408 included, 408 analyzed
Selective reporting (reporting bias)	High risk	Did not report the frequency of diarrhea, the degree of dehydration and the laboratory test results based on the methods described in the clinical trial registry (Registry number: ChiCTR-IPR-15007369)
Other bias	Unclear risk	The baseline is balanced between the treatment and control groups. However, the source of funding is not mentioned

Zakordonets 2016

Methods	A prospective, randomized, controlled, open-label study Withdrawal/Loss to follow-up: 41 eligible, 40 were randomized into 2 groups, 40 completed the study ITT: N/A Period of follow-up: During the course of antibiotic (7-14 days)
Participants	N = 40

Zakordonets 2016 *(Continued)*

	Diagnosis: Meningococcal disease (n = 2); acute bacterial tonsillitis (n = 33); pseudotuberculosis (n = 2); Lyme disease (n = 3) Country: Ukraine Setting: Inpatient Age: 3-17 years (3-14 years in methods section)
Interventions	Probiotic: Symbiter acidophilus concentrated (multiprobiotic),1 sachet/dose once a day. One sachet of multiprobiotic consists of the following (CFU/cm^3): *Lactobacilli:* 1.0x10^9;*Lactococci*: 1.0x10^9; *Bifidobacterium*: 1.0x10^8; propionate-oxidising bacteria: 3.0x10^7; acetic acid bacteria: 1.0x10^5.The total dose is 2 trillion CFUs per day confirmed by email Antibiotics: Ceftriaxone
Outcomes	ID: 0 in treatment group (0/20), 6 in control group (6/20, 30%) Definition of diarrhea: Daily production of at least 3 soft or liquid stools for at least 2 consecutive days
Notes	Funding: "The study was supported by the Research and Production Company "OD Prolisok" Grant 2013-20/03/2014 to Bogomolets National Medical University"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Children were randomly assigned to two groups by using a computer-generated randomization list"
Allocation concealment (selection bias)	Unclear risk	"The allocation schedule was list fully concealed from doctors working in the Clinical Department of Children's Infectious Diseases who recruited patients to the study." However, there could be other parties, like nurses and residents, involved in recruitment
Blinding (performance bias and detection bias) All outcomes	High risk	Given this was an "open-label study design", participants and researchers were not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	40 patients were randomized into 2 groups. "All 40 patients completed the antibiotic treatment period and intervention period"
Selective reporting (reporting bias)	Unclear risk	There is no published protocol; therefore, there is not enough information to assess reporting bias
Other bias	High risk	The study was supported by the Research and Production Company "OD Prolisok"

Zhang 2015

Methods	Randomized, but method not specified Withdrawal/Loss to follow-up: 11 in total (11/205, 5.4%), 3 in treatment (3/105, 2.9%), 8 in control (8/100, 8.0%) ITT: N/A

Zhang 2015 *(Continued)*

	Period of follow-up: Not reported
Participants	N = 205, 194 received the full course of treatment Diagnosis: H. pylori infection Country: China Setting: Outpatient Age: 22 months-16 years (mean 8.51±3.60 years)
Interventions	Probiotic: *S. boulardii* (500 mg per day, 10 billion CFUs) Antibiotic: Triple eradication therapy (omeprazole+amoxicillin+clarithromycin, or omeprazole+metronidazole+clarithromycin if penicillin allergy)
Outcomes	ID: 12 in treatment (12/102, 11.8%), severe 1 (1/12, 8%); 26 in control (26/92, 28.3%), severe 5 (5/26, 19%) Definition of diarrhea: An increase in the frequency of bowel movements to >3/day or a decrease in stool consistency (Bristol stool scale 5 or 6)
Notes	Funding: Not reported. However, the corresponding author is a consultant for United pharmaceuticals and Biocodex.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgement of "Low risk" or "High risk" "194 H. pylori positive children were randomized in 2 groups" but no further explanation provided
Allocation concealment (selection bias)	Unclear risk	Unclear. "Our study does have some limitation as it is an open study." No allocation concealment procedure outlined
Blinding (performance bias and detection bias) All outcomes	High risk	Blinding not done.. "The findings of this trial need to be confirmed with a prospective double blind study in which diagnosis is based on histology and culture"
Incomplete outcome data (attrition bias) All outcomes	Low risk	205 patients randomized, 11 lost to follow-up (3 in treatment group, 8 in control group), 194 analyzed. Attrition numbers low
Selective reporting (reporting bias)	Unclear risk	No protocol published. There is not enough information to assess reporting bias
Other bias	Unclear risk	Source of funding not reported. Yvan Vandenplas, who is a consultant for United Pharmaceuticals and Biocodex, is the corresponding author of the study

Zhao 2014

Methods	Randomized controlled trial Withdrawal/Loss to follow-up: 0

Zhao 2014 *(Continued)*

	ITT: N/A Period of follow-up: End of antibiotic therapy
Participants	N = 240 Diagnosis: patients with H. pylori infection diagnosed by 13^C breath test Country: China Setting: Outpatient and inpatient Age: 7±2 years in treatment group; 9±2 years in control group
Interventions	Probiotics: *Saccharomyces boulardii* 250mg twice a day (10 billion CFUs per day) Antibiotics: Amoxicillin, clarithromycin, omeprazole
Outcomes	ID: 27 in treatment (27/120, 22.5%), 47 in control (47/120, 39.2%) Definition of diarrhea: Not reported.
Notes	Funding source not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table method
Allocation concealment (selection bias)	High risk	Allocation concealment not reported. However, we assumed that risk of bias was high for allocation concealment because probiotic group received 4 medications while the control group received 3 medications
Blinding (performance bias and detection bias) All outcomes	High risk	Not blinded. The control group is given triple therapy. The treatment group is given triple therapy plus probiotics
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the trial. The total sample size is 240 (120 in each group). All 240 were analysed
Selective reporting (reporting bias)	Unclear risk	The protocol was not published
Other bias	Unclear risk	Funding source not mentioned

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

Zheng 2012 *(Continued)*

	Diagnosis: Pneumonia Country: China Setting: Hospital, in-patient, 7 sites Age: average age in months: 13.99
Interventions	Probiotics: *Clostridium Butyricum* (50 million CFUs), *Bifidobacterium* (500 million CFUs) 4 packets a day 2.2 billion CFUs/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
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/)(ChiCTR-PRC-10001179)
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), *Helicobacter Pylori* (HP)
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)

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
Islek 2015	The intervention is synbiotic, not probiotic
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
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

Study	Reason for exclusion
Morrow 2010	Not a pediatric population
Nista 2004	Not a pediatric population
Pancheva 2009	Incidence of vomiting and diarrhea were reported together
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
Wenus 2008	Did not include children
Witsell 1995	Not a pediatric population
Zoppi 2001	Primary outcome not diarrhea. A study of how antibiotics effect the gut flora

AAD: antibiotic-associated diarrhea

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

NCT02722993

Trial name or title	Efficacy of a Probiotic Product in Children With Antibiotic-associated Gastrointestinal Disorders
Methods	Randomized
Participants	Children at the age of 1-11 years that have been prescribed antibiotic treatment
Interventions	Probiotics vs placebo
Outcomes	Number of loose/watery stools (Time frame: 19-26 days)
Starting date	February 3, 2016
Contact information	Piotr Socha, Prof. Children's Memorial Health Institute, Warzaw, Poland (No contact information provided)
Notes	Actual enrollment: 117 participants. Actual study completion Date :May 8, 2017

NCT02765217

Trial name or title	Effect of Lactobacillus Reuteri DSM 17938 to Prevent Antibiotic-associated Diarrhea in Children: Prospective, Multi-center, Randomize, Parallel Group Placebo Controlled Clinical Trial
Methods	Randomized
Participants	Children receiving amoxicilline-clavulanic acid (50-90 mg/kg/day, twice daily) due to acute otitis media or acute sinusitis, with aged from 6 months to 18 years
Interventions	3 study arms: group 1 (Lactobacillus reuteri DSM 17938 with 5 drops vs Amoxicillin-Clavulanic acid); group 2 (placebo vs Amoxicillin-Clavulanic acid); group 3 (Lactobacillus reuteri DSM 17938 with 2*5 drops vs Amoxicillin-Clavulanic acid)
Outcomes	Incidence of antibiotic associated diarrhea (Time Frame: 8 weeks time period after 1st day of antibiotic use)
Starting date	June 1, 2017
Contact information	Ener C Dinleyici, MD; enercagri@gmail.com
Notes	Estimated enrollment: 1440

NCT02993419

Trial name or title	Bacillus Particles Prevent More Children's Antibiotic-associated Diarrhea (AAD), Randomized, Double-blind, Controlled Clinical Trial
Methods	A prospective, multicenter, randomized, double-blind, placebo-controlled clinical study
Participants	Participants aged from 1 month to 3 years old, with diagnosed lower respiratory tract infection
Interventions	Treatment group with Bacillus licheniformis Intervention; Control group with placebo Intervention
Outcomes	Record daily stool frequency, shape observation excrement

NCT02993419 *(Continued)*

Starting date	December 2016
Contact information	No contacts provided
Notes	Estimated enrollment: 480

NCT03181516

Trial name or title	Efficacy and Safety of BB-12 Supplemented Strawberry Yogurt For Healthy Children on Antibiotics
Methods	Randomized
Participants	Child aged from 3 to 12 years, with taking a penicillin or cephalosporin class antibiotic regimen for 10 days for a respiratory infection
Interventions	Bifidobacterium animalis subsp. lactis BB-12-supplemented yogurt vs yogurt without Bifidobacterium animalis subsp. lactis BB-12
Outcomes	Diarrhea (Time Frame: 14 days)
Starting date	September 30, 2017
Contact information	Dan Merenstein, MD; djm23@georgetown.edu
Notes	Estimated enrollment: 300

NCT03334604

Trial name or title	The Effect of a Multispecies Probiotic on Reducing the Incidence of Antibiotic-associated Diarrhoea in Children
Methods	Randomized
Participants	Children aged 6 months to 18 years, undergoing antibiotic treatment
Interventions	Multispecies probiotic (consisting of Bifidobacterium bifidum W23, Bifidobacterium lactis W51, Lactobacillus acidophilus W37, Lactobacillus acidophilus W55, Lactobacillus paracasei W20, Lactobacillus plantarum W62, Lactobacillus rhamnosus W71 and Lactobacillus salivarius W24 at a dose of 5x10^9 Colony Forming Units (CFU), twice daily, orally) vs placebo
Outcomes	Incidence of antibiotic-associated diarrhea (Time Frame: Up to 7th day after antibiotic cessation
Starting date	February 16, 2018
Contact information	Hanna Szajewska, MD, PhD; hania@ipgate.com
Notes	Estimated enrollment: 350

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	33	6352	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.36, 0.56]
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	19	2335	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.37, 0.67]
1.3 Incidence of Diarrhea: No treatment control	12	3244	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.26, 0.47]
2 Incidence of diarrhea: Inpatient versus outpatient	21	3949	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.31, 0.61]
2.1 Inpatient	10	1469	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.26, 0.45]
2.2 Outpatient	11	2480	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.33, 0.88]
3 Incidence of diarrhea: Diagnosis	27	4847	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.34, 0.55]
3.1 H. pylori	6	700	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.35, 0.64]
3.2 Respiratory Infections	6	1064	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.33, 0.61]
3.3 Mixed	15	3083	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.27, 0.67]
4 Incidence of diarrhea: Probiotic species	33	6352	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.36, 0.56]
4.1 *Lactobacillus rhamnosus* (strains: GG, ATCC53103 and E/N, Oxy, Pen)	6	686	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.24, 0.55]
4.2 *L. acidophilus* & *L. bulgaricus*	1	38	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.61, 1.50]
4.3 *L. acidophilus* and *Bifidobacterium infantis*	1	18	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.18, 1.21]
4.4 *L. sporogenes*	1	98	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.29, 0.77]
4.5 *Saccharomyces boulardii*	9	3165	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.24, 0.54]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.6 *Bifidobacterium. lactis* & *Streptococcus. thermophilus*	1	157	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.29, 0.95]
4.7 *Bacillus clausii*	1	323	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.11, 1.62]
4.8 *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]
4.9 *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]
4.10 *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]
4.11 *Lactobacillus rhamnosus GG*, *Bifidobacterium animalis subsp. Lactis Bv-12*, *L. acidophilus* LA-5	1	70	Risk Ratio (M-H, Random, 95% CI)	0.08 [0.00, 1.39]
4.12 *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]
4.13 *Lactobacillus reuteri* DSM 17938	2	344	Risk Ratio (M-H, Random, 95% CI)	1.68 [0.76, 3.72]
4.14 *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]
4.15 *L. casei* DN-114 001	1	86	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.18, 2.84]
4.16 *Clostridium Butyricum* and *Bifidobacterium*	1	372	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.26, 0.83]
4.17 *Lactobacillus plantarum DSM 9843*	1	438	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.24, 1.86]
4.18 *Lactobacilli and Lactococci, Bifidobacterium, propionate-oxidising bacteria and acetic acid bacteria*	1	40	Risk Ratio (M-H, Random, 95% CI)	0.08 [0.00, 1.28]
4.19 *Lactobacillus sporegens, Streptococcus faecalis, clostridium butyricum and Bacillus mesentericus*	1	100	Risk Ratio (M-H, Random, 95% CI)	0.14 [0.01, 2.70]

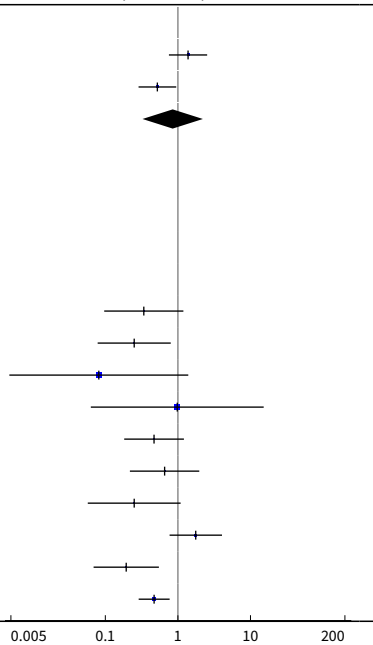
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5 Incidence of diarrhea: Single strain versus multi strain	33	6352	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.36, 0.56]
5.1 Single Strain	20	4900	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.32, 0.56]
5.2 Multi Strain	13	1452	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.37, 0.75]
6 Incidence of diarrhea: Probiotic dose	32	6252	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.36, 0.57]
6.1 ≥5 billion CFUs of probiotic/day	20	4038	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.30, 0.46]
6.2 <5 billion CFUs of probiotic/day	12	2214	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.46, 1.01]
7 Incidence of diarrhea: Definition of diarrhea	27	6499	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.31, 0.54]
7.1 3 or more watery/liquid stools for more than 2 days	2	317	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.02, 11.75]
7.2 3 or more loose/watery/liquid stools per day for at least 2 consecutive days	13	1873	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.25, 0.50]
7.3 ≥3 watery/liquid stools per 24 hours	9	2748	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.31, 0.76]
7.4 ≥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]
7.5 ≥2 loose/watery/liquid stools for more than 2 days	2	478	Risk Ratio (M-H, Random, 95% CI)	0.12 [0.05, 0.27]
7.6 ≥2 liquid stools per 24 hr	2	345	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.32, 1.30]
7.7 ≥1 abnormally loose bowel movement per 24 hrs	1	38	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.61, 1.50]
7.8 2 or more BM over the patient's normal	1	372	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.26, 0.83]
7.9 "Any of Above (Fox)"	1	70	Risk Ratio (M-H, Random, 95% CI)	0.04 [0.01, 0.27]
8 Incidence of diarrhea: Strictness of definition (mild vs moderate)	25	5408	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.32, 0.53]
8.1 Moderate diarrhea	20	4304	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.31, 0.53]

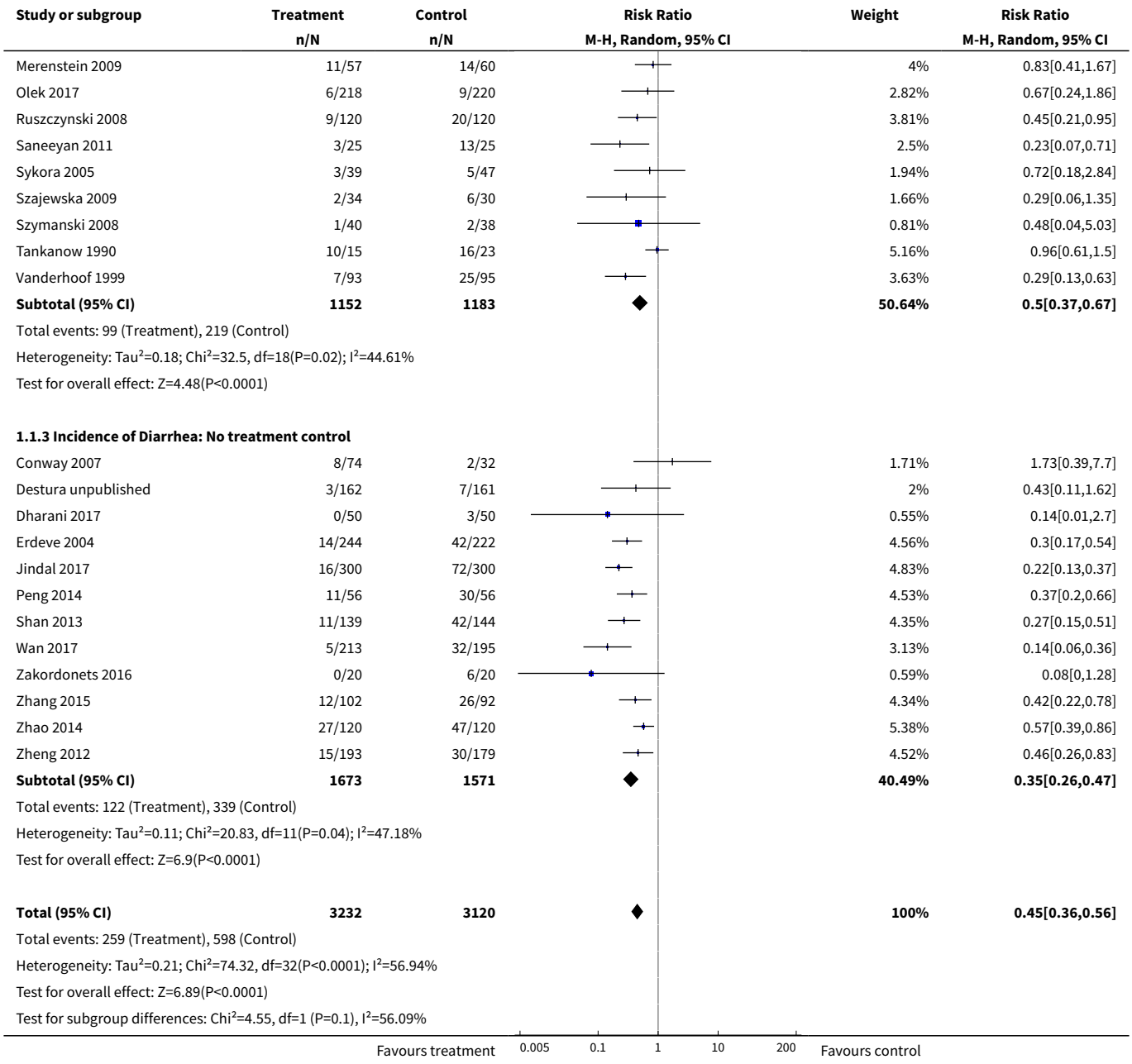
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.2 Mild diarrhea	5	1104	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.22, 0.77]
9 Incidence of diarrhea: Industry sponsorship	17	2942	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.34, 0.75]
9.1 Industry Sponsored	9	1627	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.40, 0.82]
9.2 Non-Industry	8	1315	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.18, 1.00]
10 Incidence of diarrhea: Risk of bias	33	6352	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.36, 0.56]
10.1 Low Risk	13	2170	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.37, 0.77]
10.2 High Risk	20	4182	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.31, 0.56]
11 Incidence of diarrhea: age	32	5752	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.37, 0.58]
11.1 0-2 years (≤ 24 months)	6	1127	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.26, 0.53]
11.2 > 2 years (>24 months)	26	4625	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.39, 0.66]
12 Incidence of diarrhea: Sensitivity analysis (complete case - fixed effects)	33	6352	Risk Ratio (M-H, Fixed, 95% CI)	0.43 [0.37, 0.49]
12.1 Active controlled	2	773	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.58, 1.32]
12.2 Placebo controlled	19	2335	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.39, 0.59]
12.3 No treatment control	12	3244	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.28, 0.41]
13 Incidence of diarrhea: Probiotic dose (extreme-plausible analysis)	33	7019	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.49, 0.77]
13.1 ≥5 billion CFUs of probiotic/day	20	4425	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.42, 0.70]
13.2 <5 billion CFUs of probiotic/day	13	2594	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.54, 1.20]
14 Incidence of diarrhea: Sensitivity analysis (missing outcome data - extreme plausible analysis)	33	7019	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.49, 0.77]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14.1 Active controlled	2	948	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.40, 2.86]
14.2 Placebo controlled	19	2571	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.54, 0.92]
14.3 No treatment control	12	3500	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.31, 0.66]
15 Adverse events: Complete case	24	4415	Risk Difference (M-H, Random, 95% CI)	-0.00 [-0.01, 0.01]
16 Adverse events: Same event rate assumptions analysis	24	4595	Risk Difference (M-H, Random, 95% CI)	-0.00 [-0.01, 0.01]
17 Adverse events: Risk of bias	24	4415	Risk Difference (M-H, Random, 95% CI)	-0.00 [-0.01, 0.01]
17.1 Low RoB	11	1978	Risk Difference (M-H, Random, 95% CI)	-0.02 [-0.05, 0.01]
17.2 High/Unclear	13	2437	Risk Difference (M-H, Random, 95% CI)	0.00 [-0.00, 0.00]
18 Mean duration of diarrhea: Complete case	8	1263	Mean Difference (IV, Random, 95% CI)	-0.91 [-1.38, -0.44]

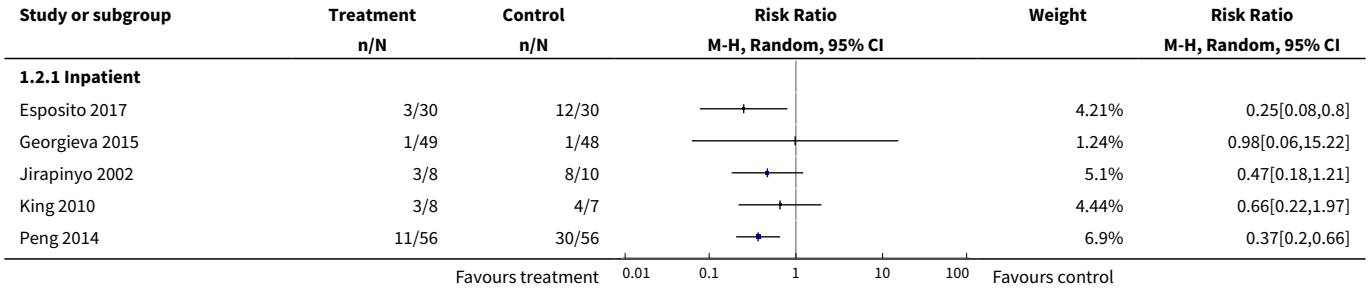
Analysis 1.1. Comparison 1 Probiotics versus control, Outcome 1 Incidence of diarrhea: Complete case.

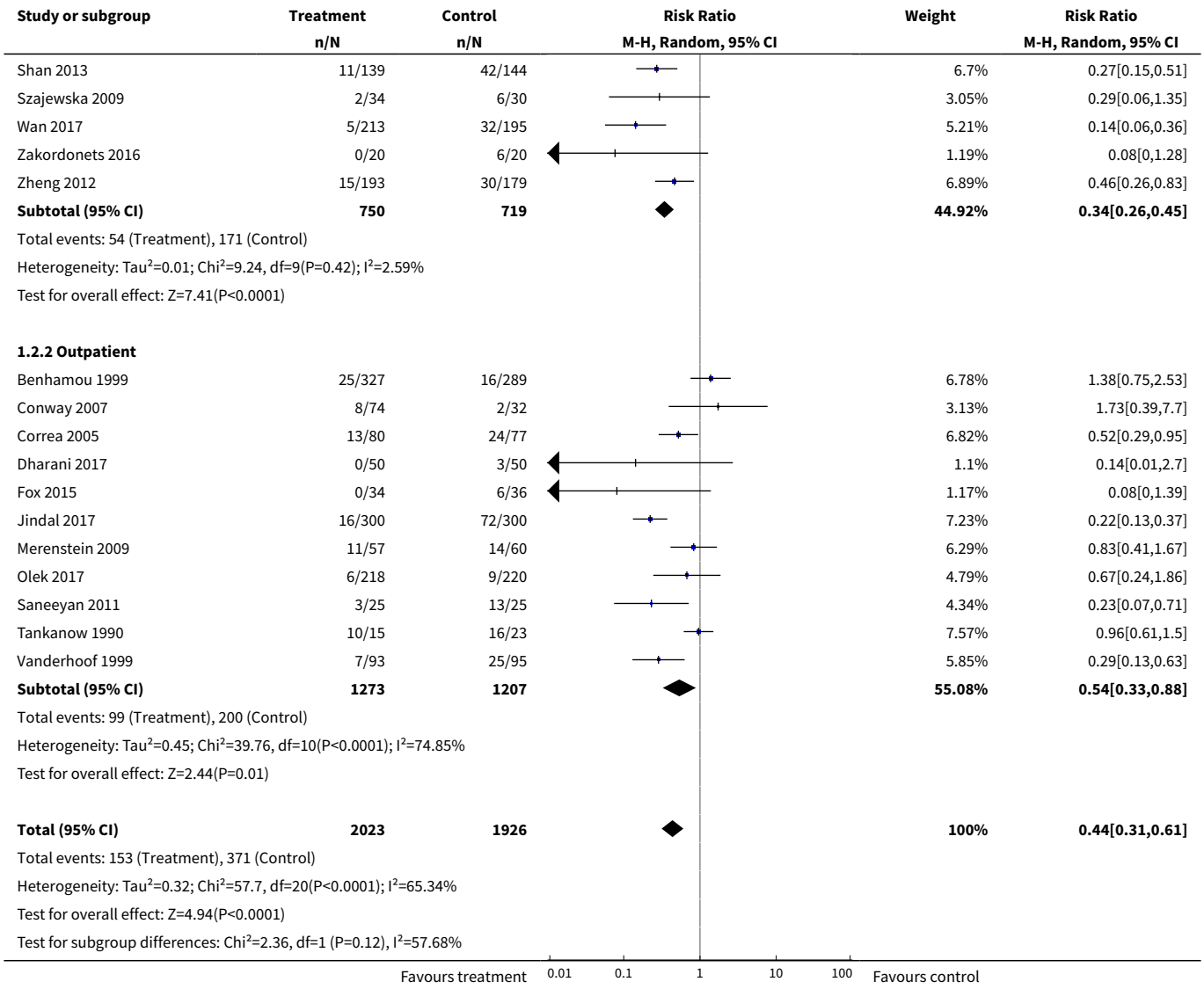
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Incidence of Diarrhea: Active controlled trials					
Benhamou 1999	25/327	16/289		4.42%	1.38[0.75,2.53]
Correa 2005	13/80	24/77		4.46%	0.52[0.29,0.95]
Subtotal (95% CI)	**407**	**366**		**8.88%**	**0.85[0.33,2.21]**
Total events: 38 (Treatment), 40 (Control)					
Heterogeneity: Tau^2=0.38; Chi^2=5.05, df=1(P=0.02); I^2=80.18%					
Test for overall effect: Z=0.34(P=0.73)					
1.1.2 Incidence of Diarrhea: Placebo controlled trials					
Arvola 1999	3/59	9/60		2.17%	0.34[0.1,1.19]
Esposito 2017	3/30	12/30		2.41%	0.25[0.08,0.8]
Fox 2015	0/34	6/36		0.58%	0.08[0,1.39]
Georgieva 2015	1/49	1/48		0.62%	0.98[0.06,15.22]
Jirapinyo 2002	3/8	8/10		3.04%	0.47[0.18,1.21]
King 2010	3/8	4/7		2.57%	0.66[0.22,1.97]
Kodadad 2013	2/33	8/33		1.74%	0.25[0.06,1.09]
Kolodziej 2018	14/123	8/124		3.46%	1.76[0.77,4.05]
Kotowska 2005	4/119	22/127		2.76%	0.19[0.07,0.55]
LaRosa 2003	14/48	31/50		4.96%	0.47[0.29,0.77]



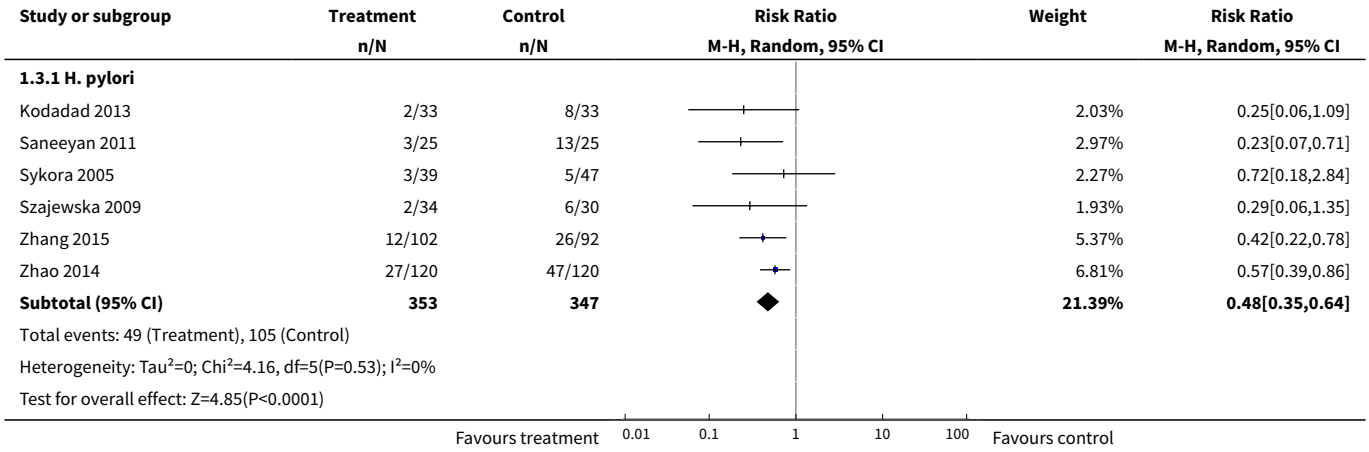


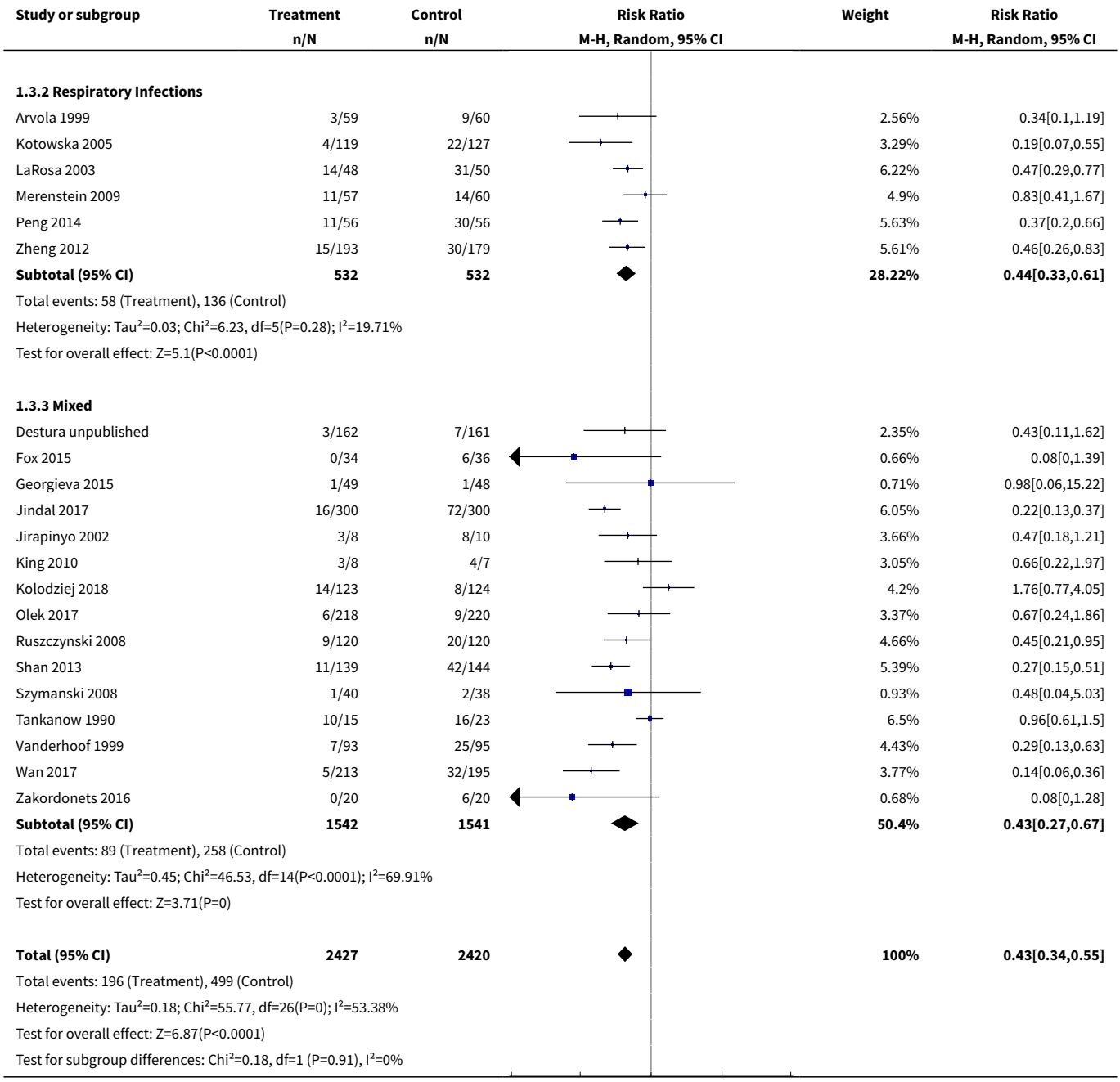
Analysis 1.2. Comparison 1 Probiotics versus control, Outcome 2 Incidence of diarrhea: Inpatient versus outpatient.



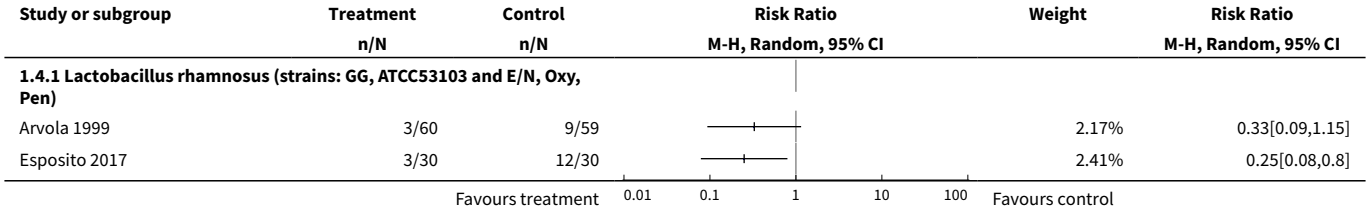


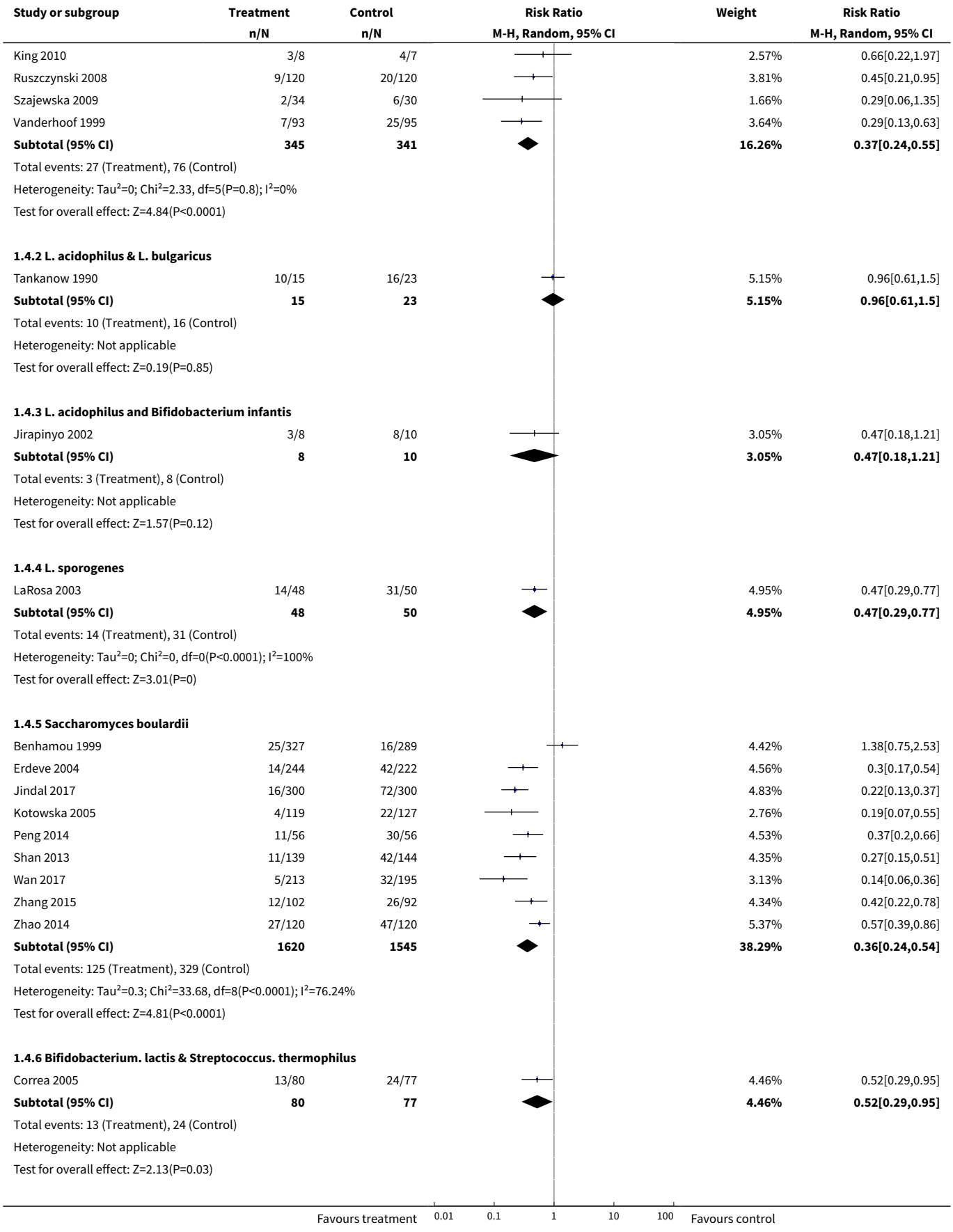
Analysis 1.3. Comparison 1 Probiotics versus control, Outcome 3 Incidence of diarrhea: Diagnosis.

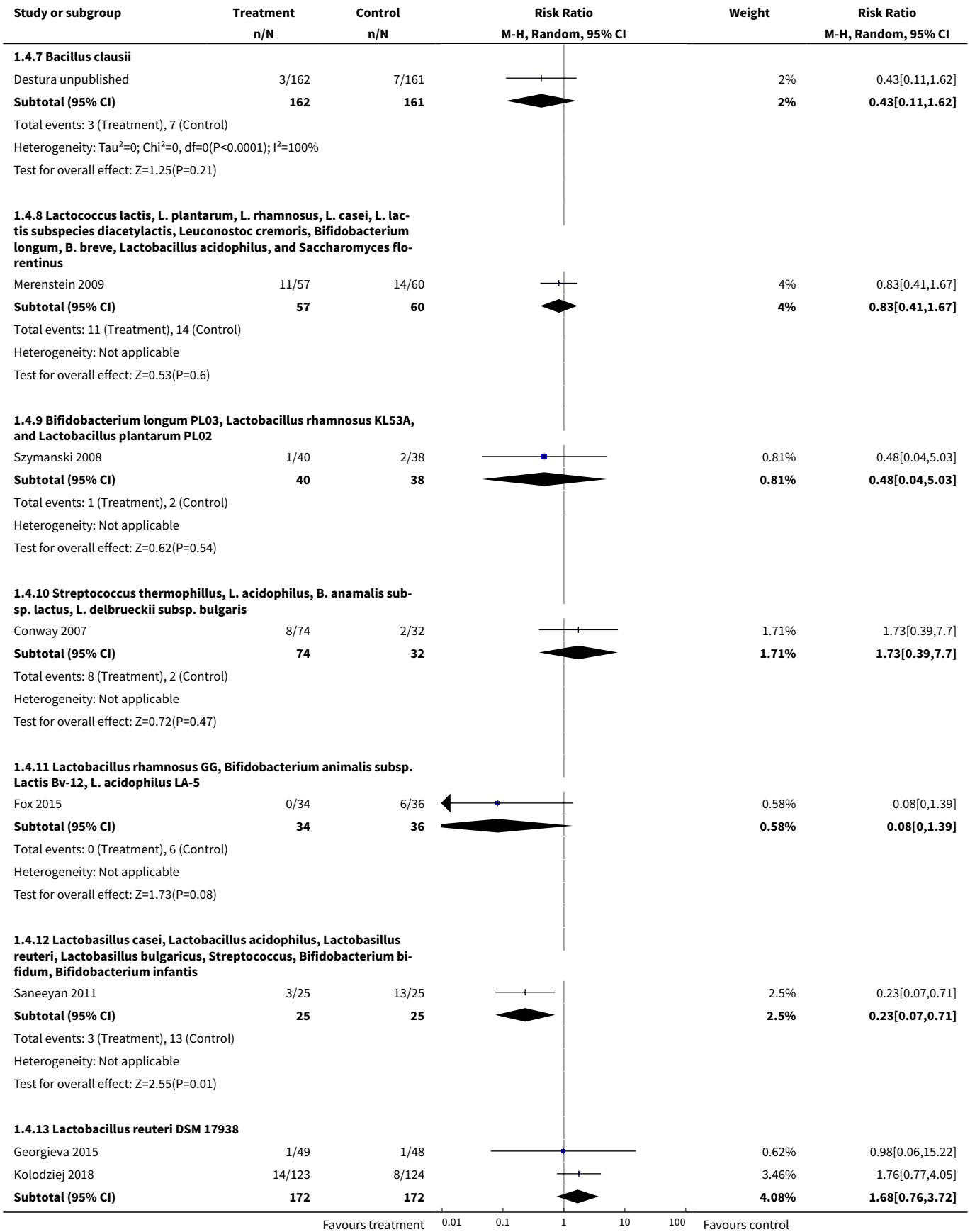


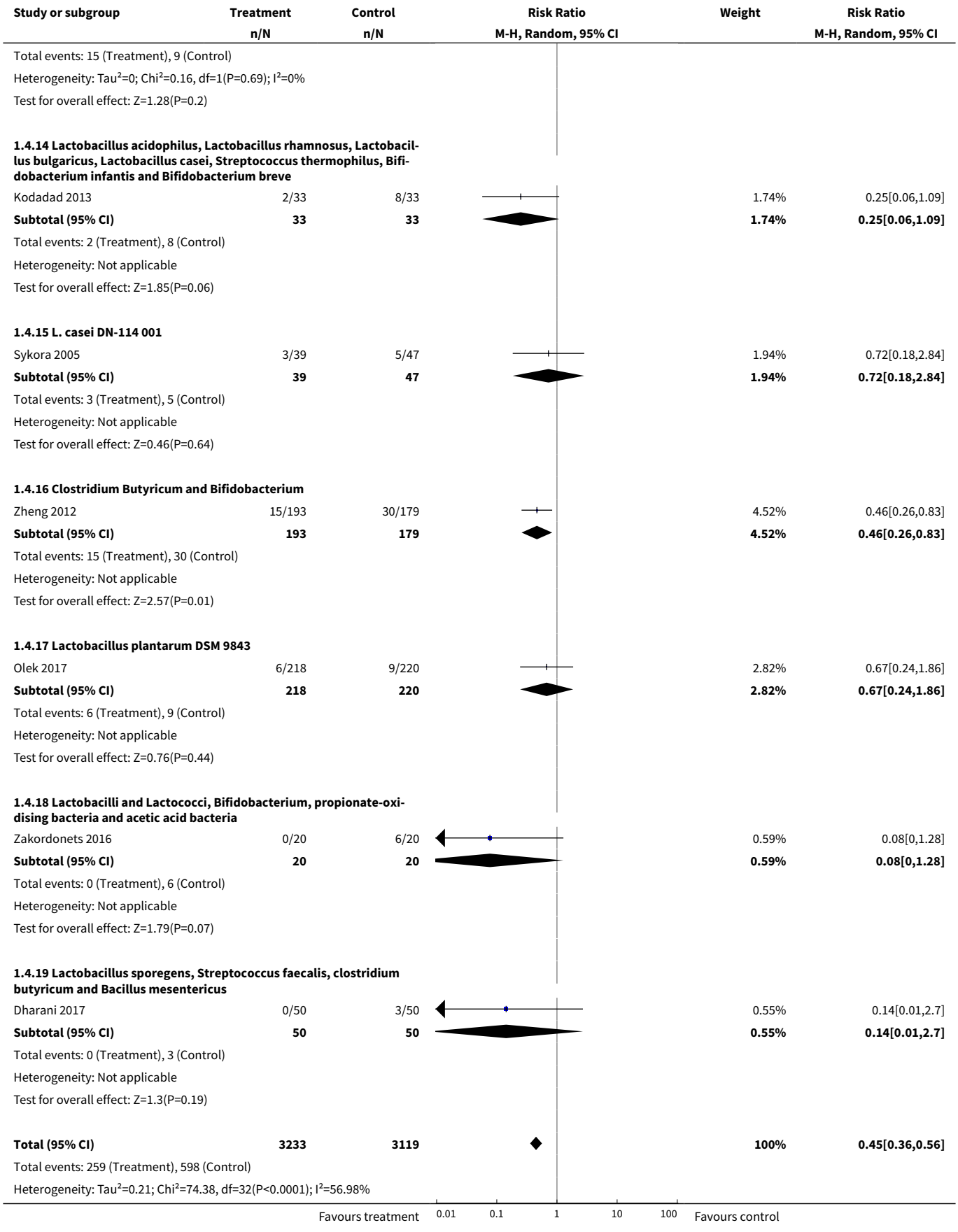


Analysis 1.4. Comparison 1 Probiotics versus control, Outcome 4 Incidence of diarrhea: Probiotic species.

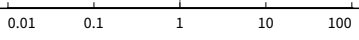






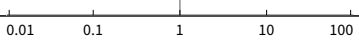


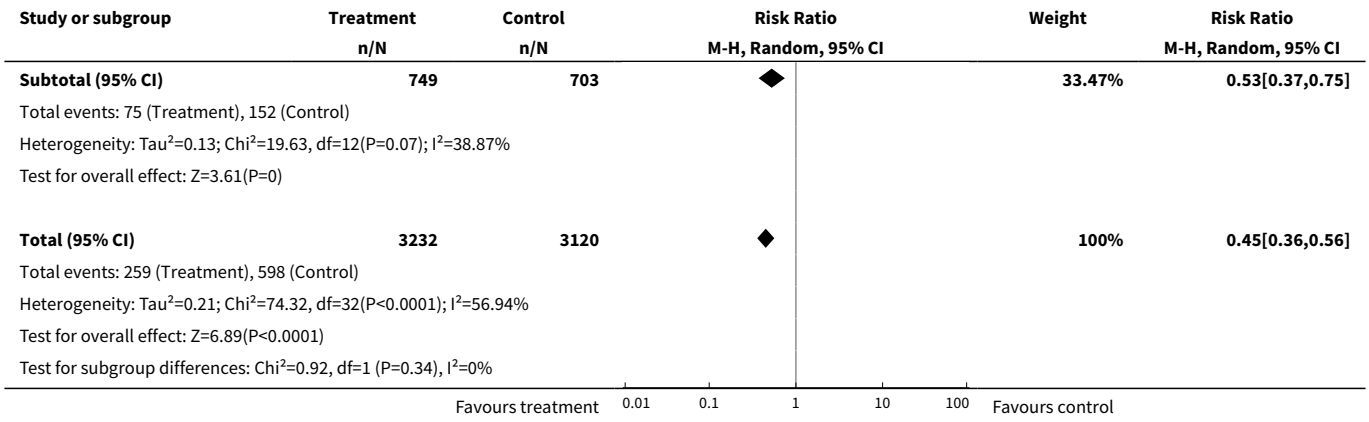
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for overall effect: Z=6.9(P<0.0001)					
Test for subgroup differences: Chi^2=33.55, df=1 (P=0.01), I^2=46.35%					



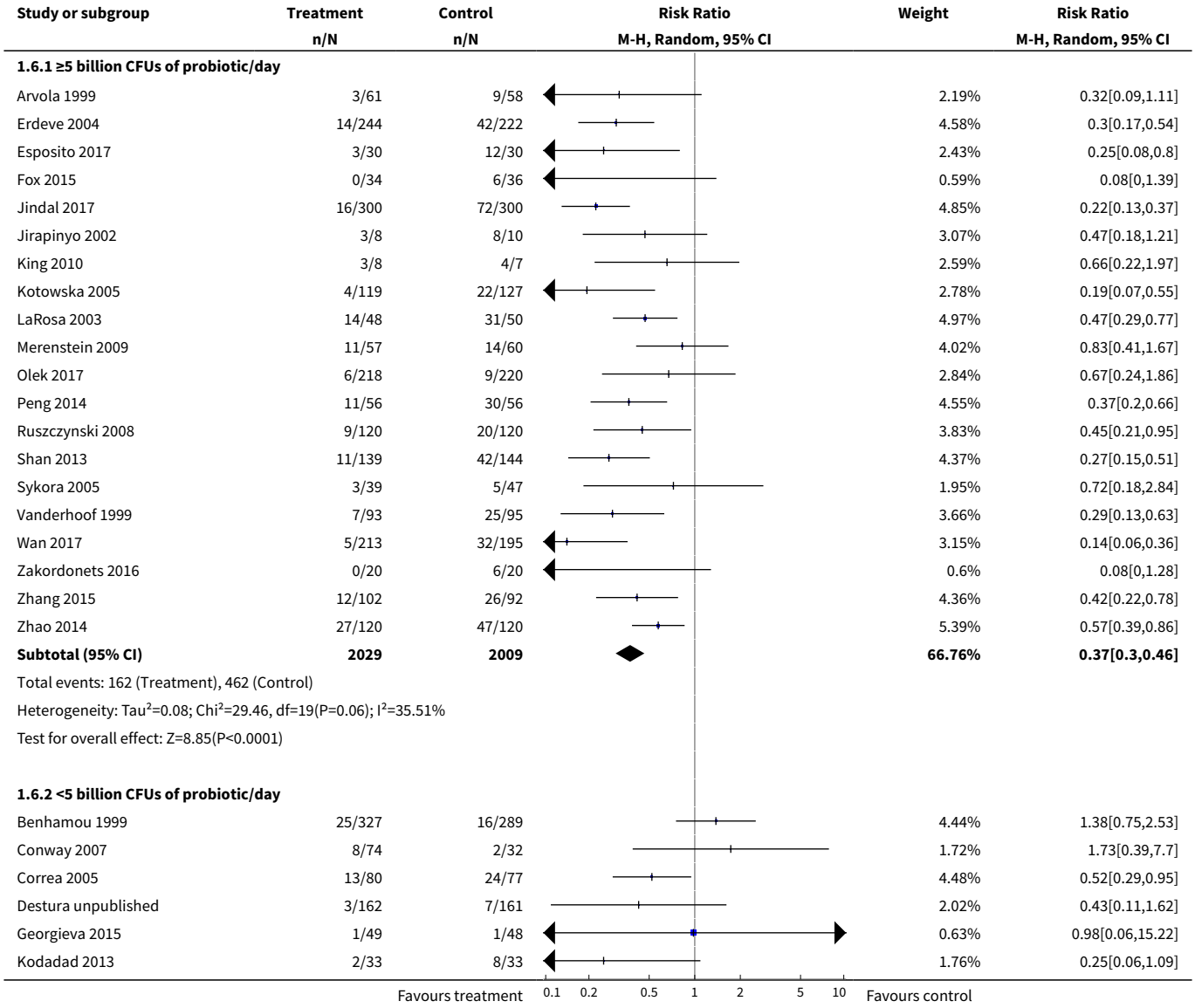
Analysis 1.5. Comparison 1 Probiotics versus control, Outcome 5 Incidence of diarrhea: Single strain versus multi strain.

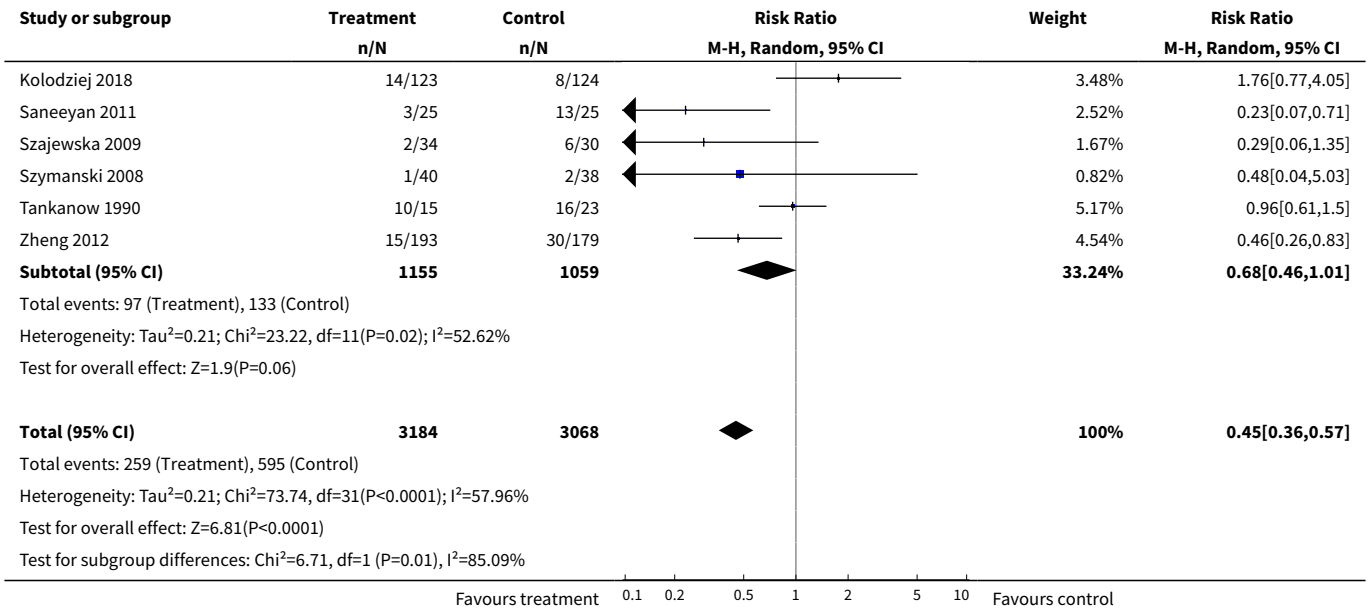
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.5.1 Single Strain					
Arvola 1999	3/59	9/60		2.17%	0.34[0.1,1.19]
Benhamou 1999	25/327	16/289		4.42%	1.38[0.75,2.53]
Destura unpublished	3/162	7/161		2%	0.43[0.11,1.62]
Erdeve 2004	14/244	42/222		4.56%	0.3[0.17,0.54]
Esposito 2017	3/30	12/30		2.41%	0.25[0.08,0.8]
Georgieva 2015	1/49	1/48		0.62%	0.98[0.06,15.22]
Jindal 2017	16/300	72/300		4.83%	0.22[0.13,0.37]
King 2010	3/8	4/7		2.57%	0.66[0.22,1.97]
Kolodziej 2018	14/123	8/124		3.46%	1.76[0.77,4.05]
Kotowska 2005	4/119	22/127		2.76%	0.19[0.07,0.55]
LaRosa 2003	14/48	31/50		4.96%	0.47[0.29,0.77]
Olek 2017	6/218	9/220		2.82%	0.67[0.24,1.86]
Peng 2014	11/56	30/56		4.53%	0.37[0.2,0.66]
Shan 2013	11/139	42/144		4.35%	0.27[0.15,0.51]
Sykora 2005	3/39	5/47		1.94%	0.72[0.18,2.84]
Szajewska 2009	2/34	6/30		1.66%	0.29[0.06,1.35]
Vanderhoof 1999	7/93	25/95		3.63%	0.29[0.13,0.63]
Wan 2017	5/213	32/195		3.13%	0.14[0.06,0.36]
Zhang 2015	12/102	26/92		4.34%	0.42[0.22,0.78]
Zhao 2014	27/120	47/120		5.38%	0.57[0.39,0.86]
Subtotal (95% CI)	**2483**	**2417**		**66.53%**	**0.42[0.32,0.56]**
Total events: 184 (Treatment), 446 (Control)					
Heterogeneity: Tau^2=0.23; Chi^2=50.14, df=19(P=0); I^2=62.11%					
Test for overall effect: Z=5.88(P<0.0001)					
1.5.2 Multi Strain					
Conway 2007	8/74	2/32		1.71%	1.73[0.39,7.7]
Correa 2005	13/80	24/77		4.46%	0.52[0.29,0.95]
Dharani 2017	0/50	3/50		0.55%	0.14[0.01,2.7]
Fox 2015	0/34	6/36		0.58%	0.08[0,1.39]
Jirapinyo 2002	3/8	8/10		3.04%	0.47[0.18,1.21]
Kodadad 2013	2/33	8/33		1.74%	0.25[0.06,1.09]
Merenstein 2009	11/57	14/60		4%	0.83[0.41,1.67]
Ruszczynski 2008	9/120	20/120		3.81%	0.45[0.21,0.95]
Saneeyan 2011	3/25	13/25		2.5%	0.23[0.07,0.71]
Szymanski 2008	1/40	2/38		0.81%	0.48[0.04,5.03]
Tankanow 1990	10/15	16/23		5.16%	0.96[0.61,1.5]
Zakordonets 2016	0/20	6/20		0.59%	0.08[0,1.28]
Zheng 2012	15/193	30/179		4.52%	0.46[0.26,0.83]



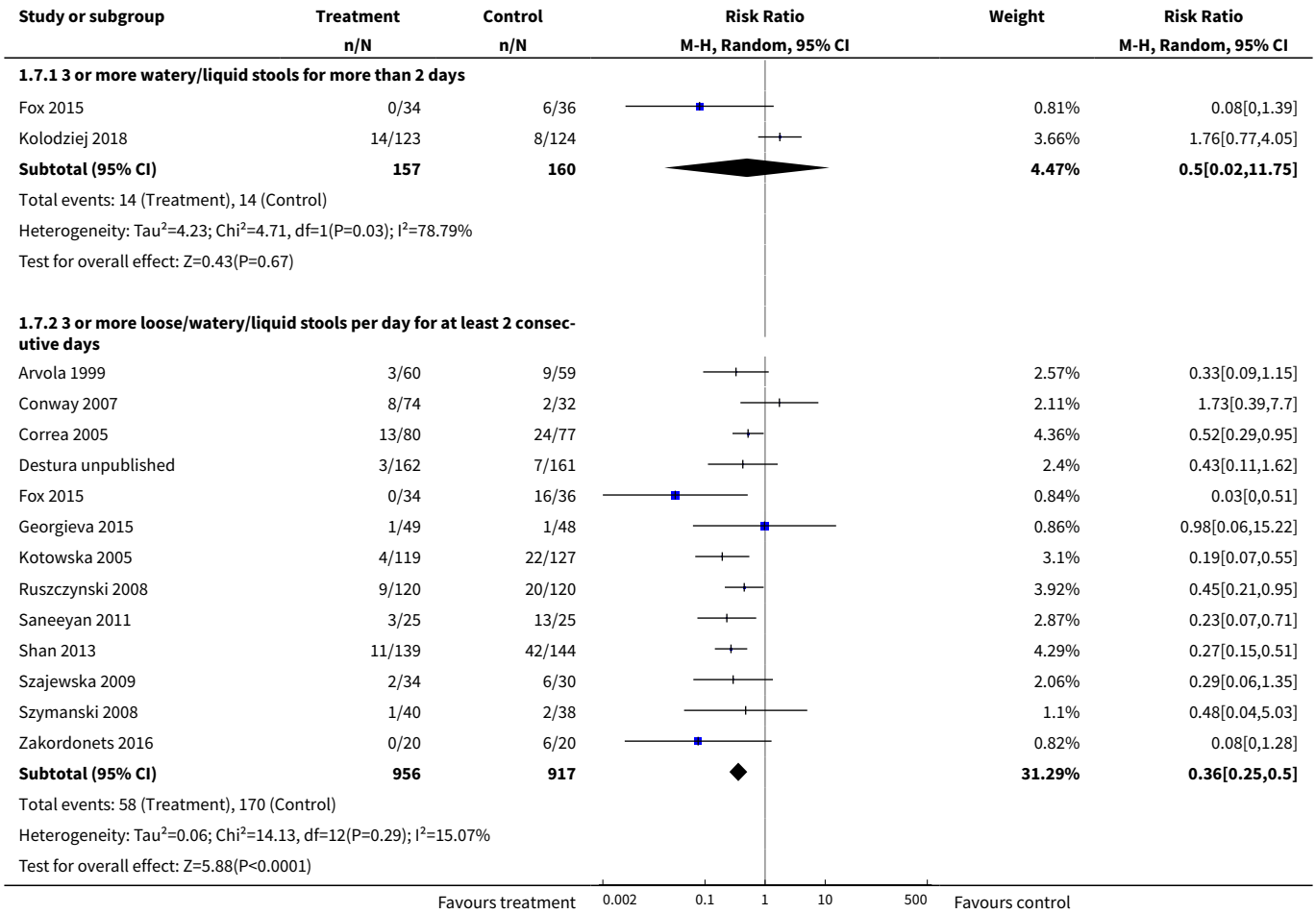


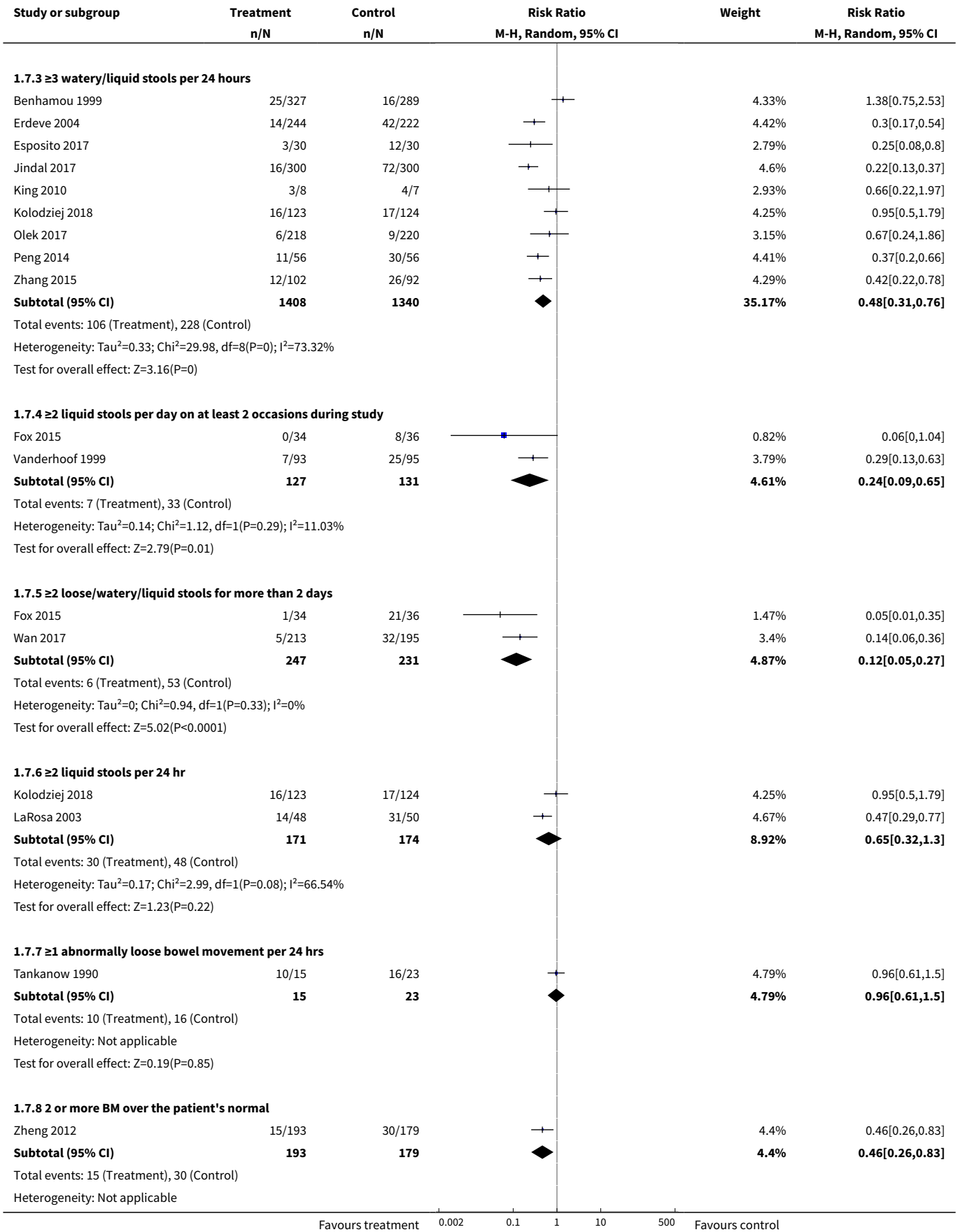
Analysis 1.6. Comparison 1 Probiotics versus control, Outcome 6 Incidence of diarrhea: Probiotic dose.

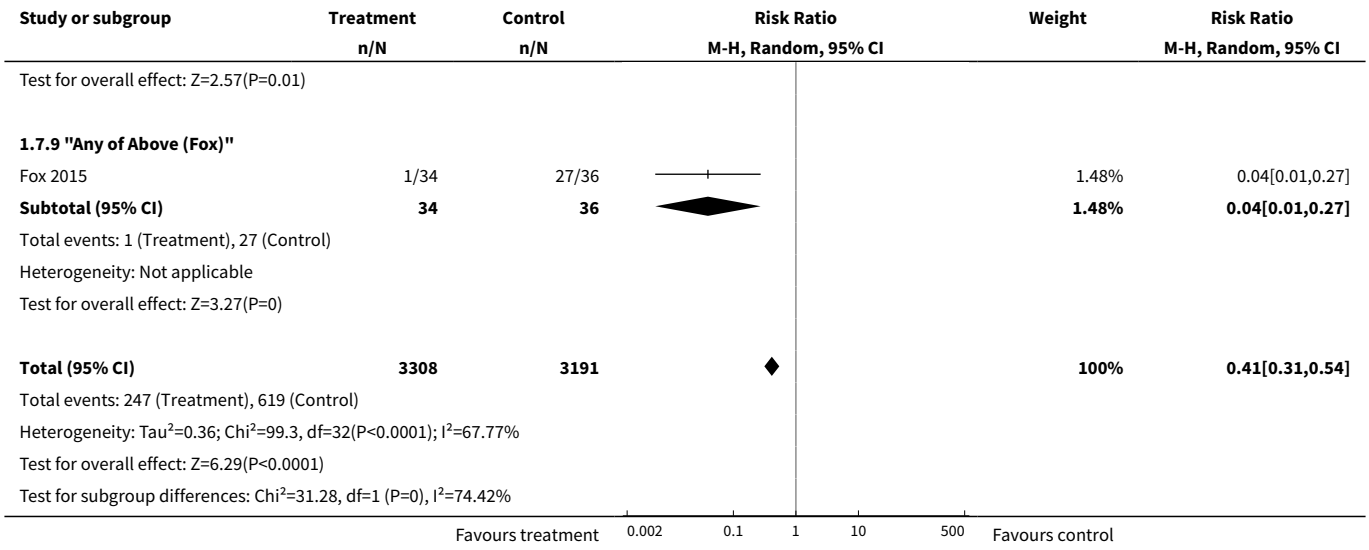




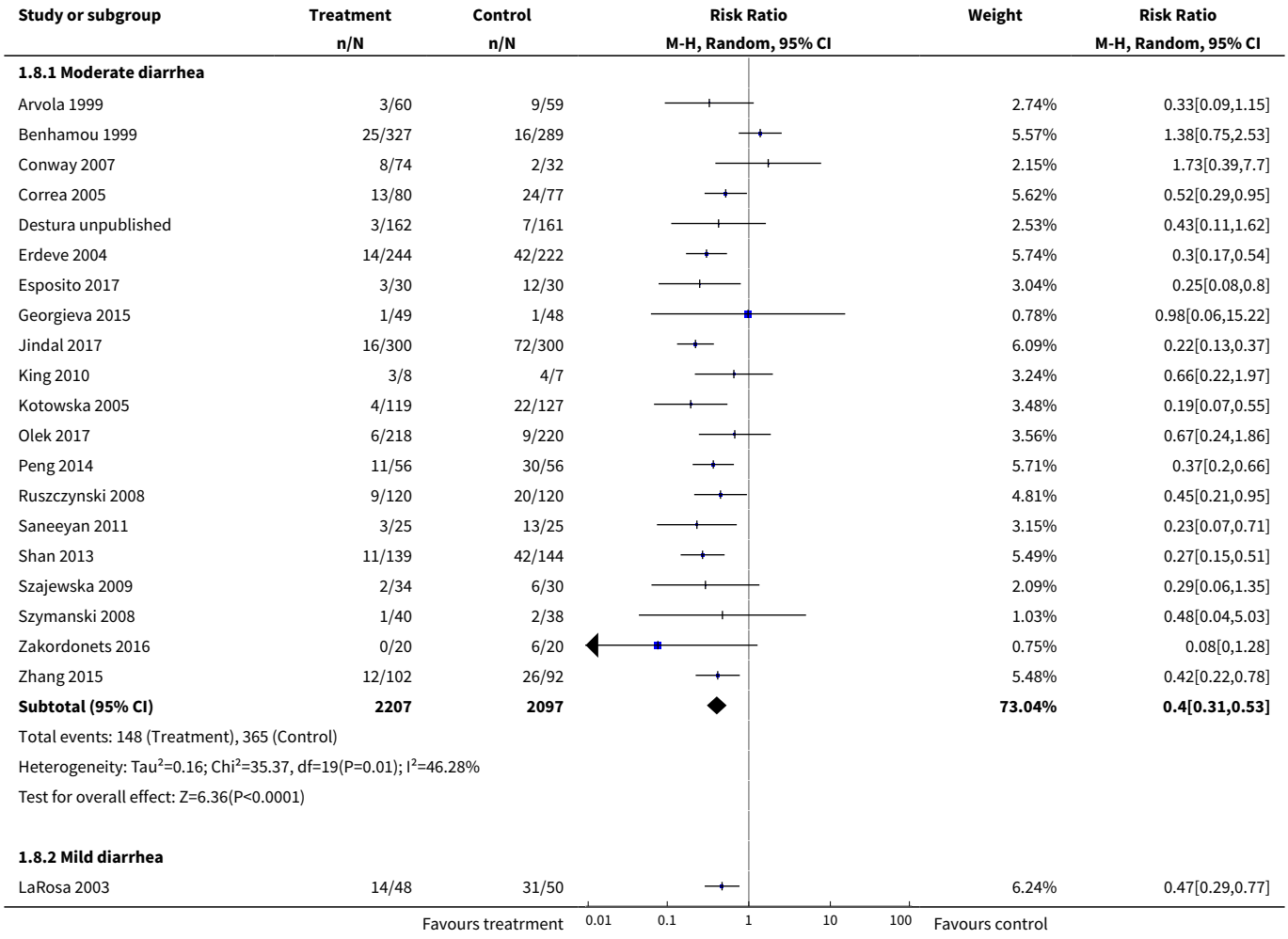
Analysis 1.7. Comparison 1 Probiotics versus control, Outcome 7 Incidence of diarrhea: Definition of diarrhea.

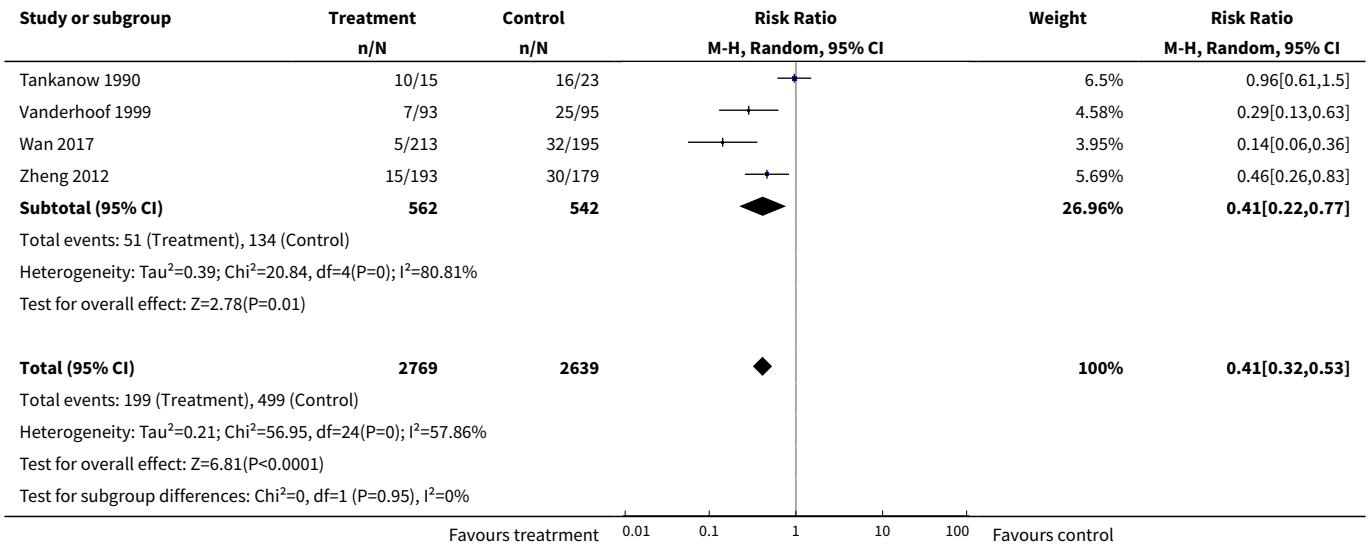




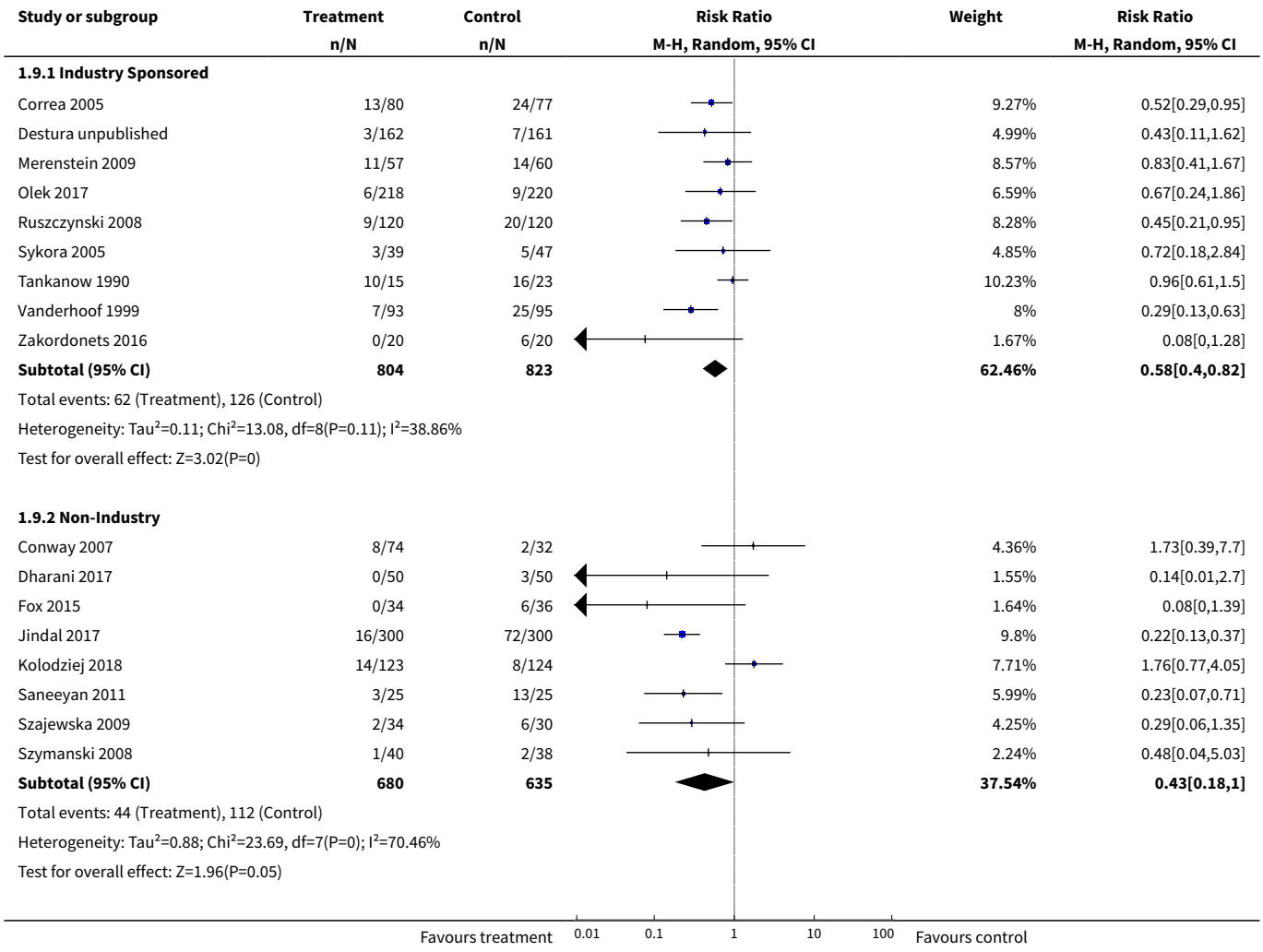


Analysis 1.8. Comparison 1 Probiotics versus control, Outcome 8 Incidence of diarrhea: Strictness of definition (mild vs moderate).





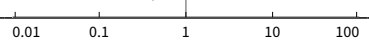
Analysis 1.9. Comparison 1 Probiotics versus control, Outcome 9 Incidence of diarrhea: Industry sponsorship.



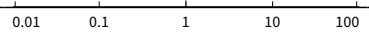
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Total (95% CI)	**1484**	**1458**		**100%**	**0.51[0.34,0.75]**
Total events: 106 (Treatment), 238 (Control)					
Heterogeneity: Tau^2=0.34; Chi^2=42.05, df=16(P=0); I^2=61.95%					
Test for overall effect: Z=3.41(P=0)					
Test for subgroup differences: Chi^2=0.41, df=1 (P=0.52), I^2=0%					

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

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.10.1 Low Risk					
Destura unpublished	3/162	7/161		2%	0.43[0.11,1.62]
Fox 2015	0/34	6/36		0.58%	0.08[0,1.39]
Georgieva 2015	1/49	1/48		0.62%	0.98[0.06,15.22]
Kodadad 2013	2/33	8/33		1.74%	0.25[0.06,1.09]
Kolodziej 2018	14/123	8/124		3.46%	1.76[0.77,4.05]
Kotowska 2005	4/119	22/127		2.76%	0.19[0.07,0.55]
LaRosa 2003	14/48	31/50		4.95%	0.47[0.29,0.77]
Merenstein 2009	11/57	14/60		4%	0.83[0.41,1.67]
Olek 2017	6/218	9/220		2.82%	0.67[0.24,1.86]
Ruszczynski 2008	9/120	20/120		3.81%	0.45[0.21,0.95]
Sykora 2005	3/39	5/47		1.94%	0.72[0.18,2.84]
Szajewska 2009	2/34	6/30		1.66%	0.29[0.06,1.35]
Szymanski 2008	1/40	2/38		0.81%	0.48[0.04,5.03]
Subtotal (95% CI)	**1076**	**1094**		**31.16%**	**0.53[0.37,0.77]**
Total events: 70 (Treatment), 139 (Control)					
Heterogeneity: Tau^2=0.13; Chi^2=17.65, df=12(P=0.13); I^2=32.01%					
Test for overall effect: Z=3.37(P=0)					
1.10.2 High Risk					
Arvola 1999	3/61	9/58		2.17%	0.32[0.09,1.11]
Benhamou 1999	25/327	16/289		4.42%	1.38[0.75,2.53]
Conway 2007	8/74	2/32		1.71%	1.73[0.39,7.7]
Correa 2005	13/80	24/77		4.46%	0.52[0.29,0.95]
Dharani 2017	0/50	3/50		0.55%	0.14[0.01,2.7]
Erdeve 2004	14/244	42/222		4.56%	0.3[0.17,0.54]
Esposito 2017	3/30	12/30		2.41%	0.25[0.08,0.8]
Jindal 2017	16/300	72/300		4.83%	0.22[0.13,0.37]
Jirapinyo 2002	3/8	8/10		3.05%	0.47[0.18,1.21]
King 2010	3/8	4/7		2.57%	0.66[0.22,1.97]
Peng 2014	11/56	30/56		4.53%	0.37[0.2,0.66]
Saneeyan 2011	3/25	13/25		2.5%	0.23[0.07,0.71]
Shan 2013	11/139	42/144		4.35%	0.27[0.15,0.51]
Tankanow 1990	10/15	16/23		5.15%	0.96[0.61,1.5]
Vanderhoof 1999	7/93	25/95		3.64%	0.29[0.13,0.63]
Wan 2017	5/213	32/195		3.13%	0.14[0.06,0.36]
Zakordonets 2016	0/20	6/20		0.59%	0.08[0,1.28]
Zhang 2015	12/102	26/92		4.34%	0.42[0.22,0.78]

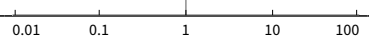


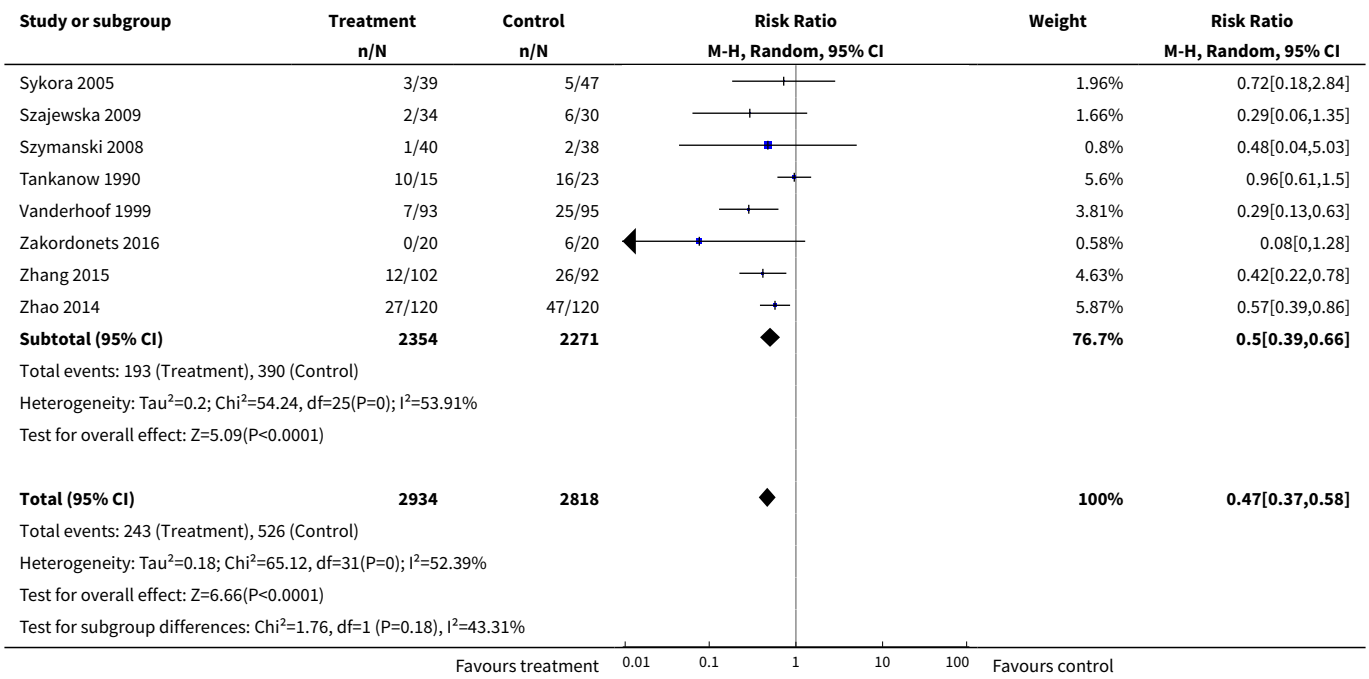
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Zhao 2014	27/120	47/120		5.37%	0.57[0.39,0.86]
Zheng 2012	15/193	30/179		4.52%	0.46[0.26,0.83]
Subtotal (95% CI)	**2158**	**2024**		**68.84%**	**0.42[0.31,0.56]**
Total events: 189 (Treatment), 459 (Control)					
Heterogeneity: Tau^2=0.25; Chi^2=55.67, df=19(P<0.0001); I^2=65.87%					
Test for overall effect: Z=5.95(P<0.0001)					
Total (95% CI)	**3234**	**3118**		**100%**	**0.45[0.36,0.56]**
Total events: 259 (Treatment), 598 (Control)					
Heterogeneity: Tau^2=0.21; Chi^2=74.45, df=32(P<0.0001); I^2=57.02%					
Test for overall effect: Z=6.9(P<0.0001)					
Test for subgroup differences: Chi^2=1.1, df=1 (P=0.3), I^2=8.7%					



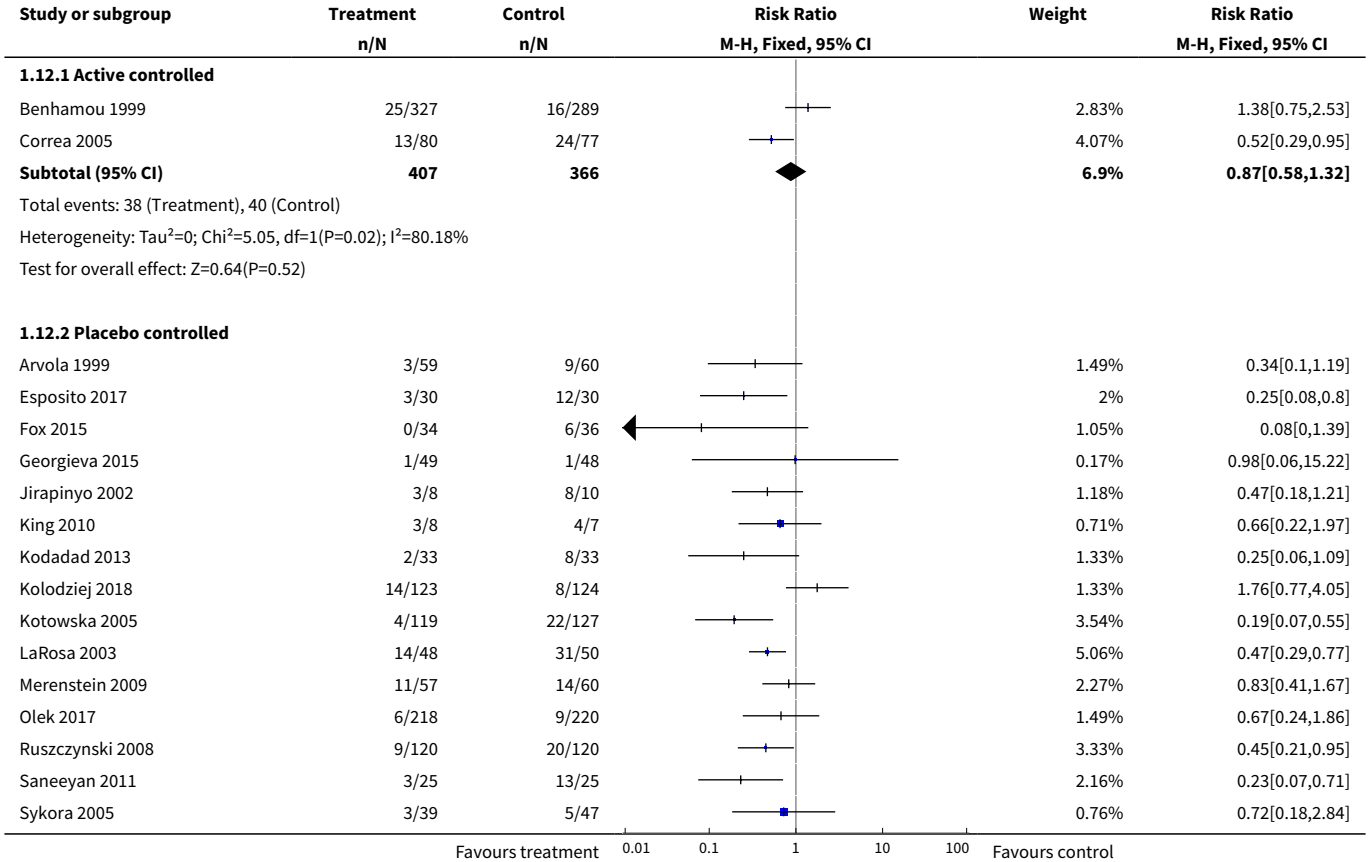
Analysis 1.11. Comparison 1 Probiotics versus control, Outcome 11 Incidence of diarrhea: age.

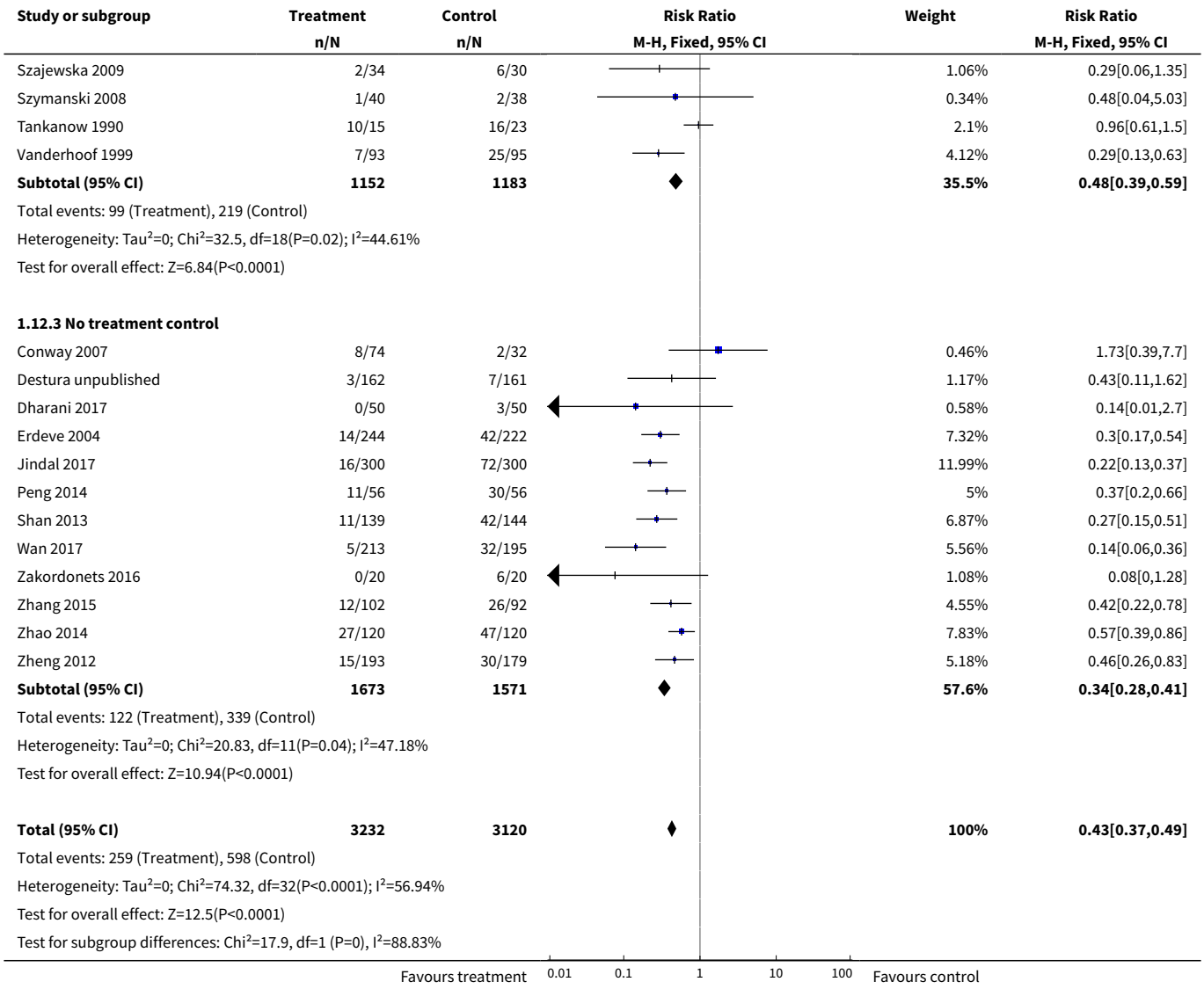
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.11.1 0-2 years (≤ 24 months)					
Correa 2005	13/80	24/77		4.76%	0.52[0.29,0.95]
Esposito 2017	3/30	12/30		2.46%	0.25[0.08,0.8]
Jirapinyo 2002	3/8	8/10		3.15%	0.47[0.18,1.21]
Peng 2014	11/56	30/56		4.85%	0.37[0.2,0.66]
Wan 2017	5/213	32/195		3.25%	0.14[0.06,0.36]
Zheng 2012	15/193	30/179		4.83%	0.46[0.26,0.83]
Subtotal (95% CI)	**580**	**547**		**23.3%**	**0.37[0.26,0.53]**
Total events: 50 (Treatment), 136 (Control)					
Heterogeneity: Tau^2=0.05; Chi^2=6.77, df=5(P=0.24); I^2=26.19%					
Test for overall effect: Z=5.49(P<0.0001)					
1.11.2 > 2 years (>24 months)					
Arvola 1999	3/61	9/58		2.21%	0.32[0.09,1.11]
Benhamou 1999	25/327	16/289		4.72%	1.38[0.75,2.53]
Conway 2007	8/74	2/32		1.72%	1.73[0.39,7.7]
Destura unpublished	3/162	7/161		2.03%	0.43[0.11,1.62]
Dharani 2017	0/50	3/50		0.54%	0.14[0.01,2.7]
Erdeve 2004	14/244	42/222		4.88%	0.3[0.17,0.54]
Fox 2015	0/34	6/36		0.57%	0.08[0,1.39]
Georgieva 2015	1/49	1/48		0.61%	0.98[0.06,15.22]
King 2010	3/8	4/7		2.63%	0.66[0.22,1.97]
Kodadad 2013	2/33	8/33		1.75%	0.25[0.06,1.09]
Kolodziej 2018	14/123	8/124		3.62%	1.76[0.77,4.05]
Kotowska 2005	4/119	22/127		2.84%	0.19[0.07,0.55]
LaRosa 2003	14/48	31/50		5.36%	0.47[0.29,0.77]
Merenstein 2009	11/57	14/60		4.22%	0.83[0.41,1.67]
Olek 2017	6/218	9/220		2.9%	0.67[0.24,1.86]
Ruszczynski 2008	9/120	20/120		4.01%	0.45[0.21,0.95]
Saneeyan 2011	3/25	13/25		2.55%	0.23[0.07,0.71]
Shan 2013	11/139	42/144		4.64%	0.27[0.15,0.51]



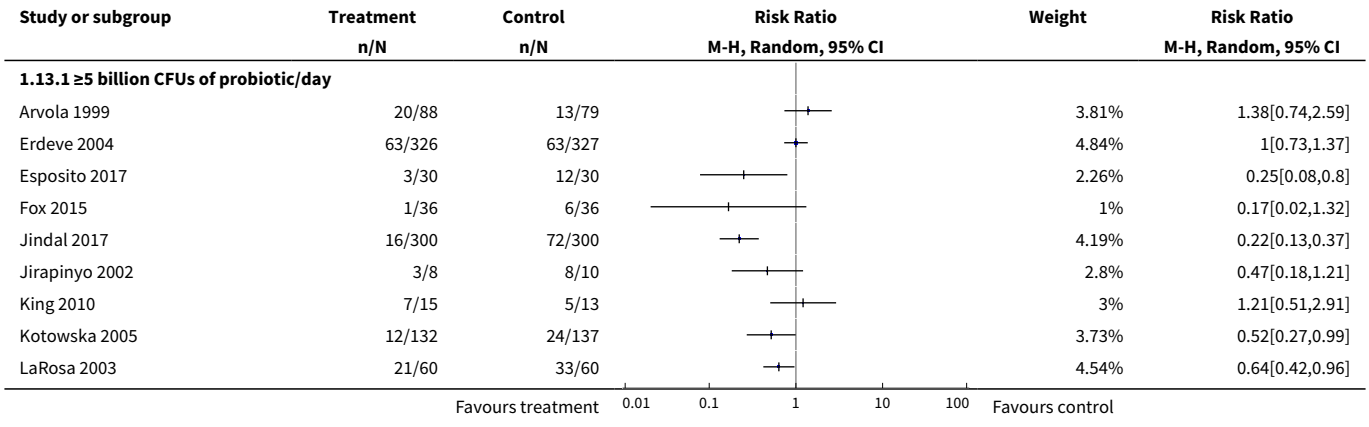


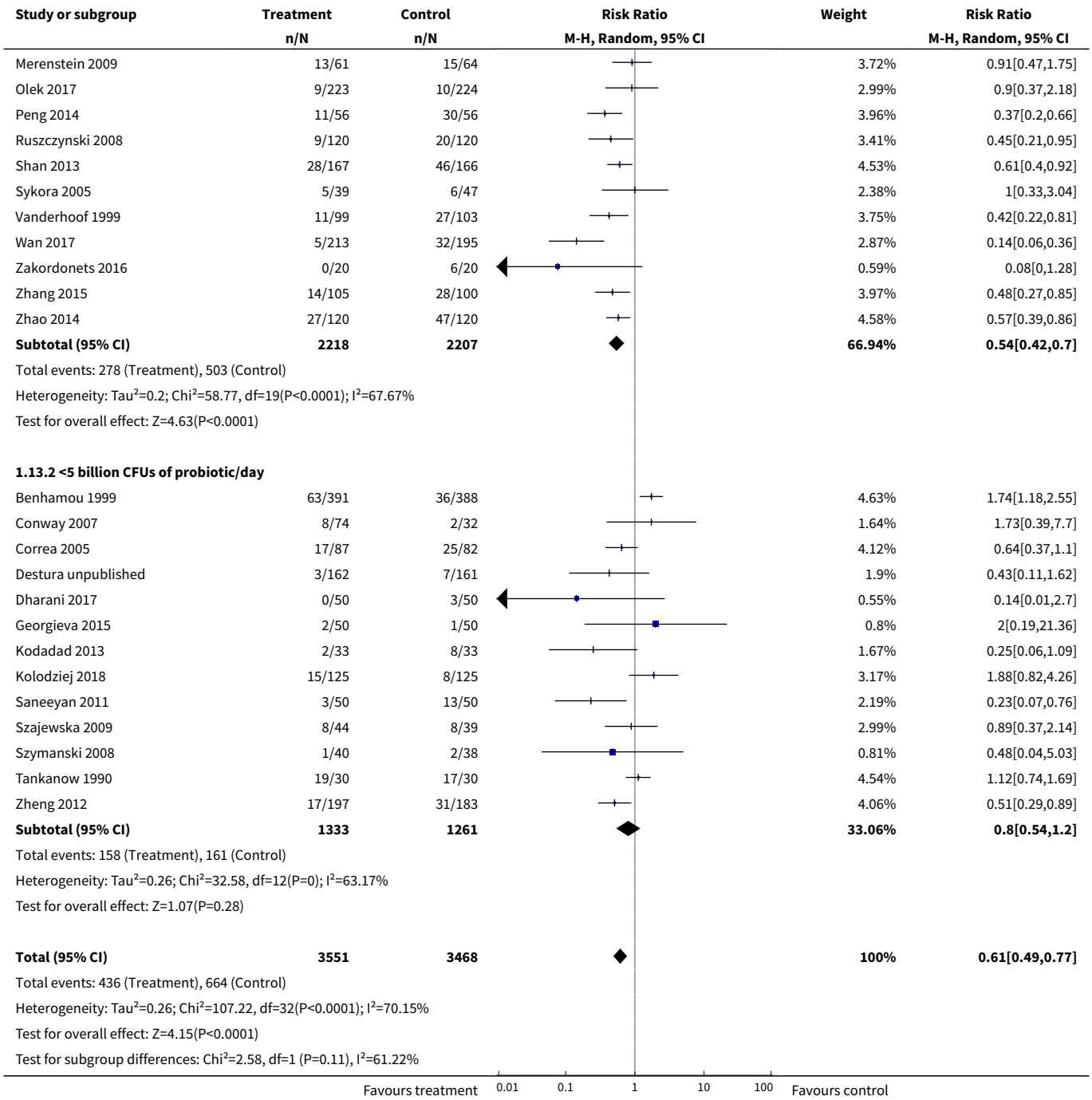
Analysis 1.12. Comparison 1 Probiotics versus control, Outcome 12 Incidence of diarrhea: Sensitivity analysis (complete case - fixed effects).



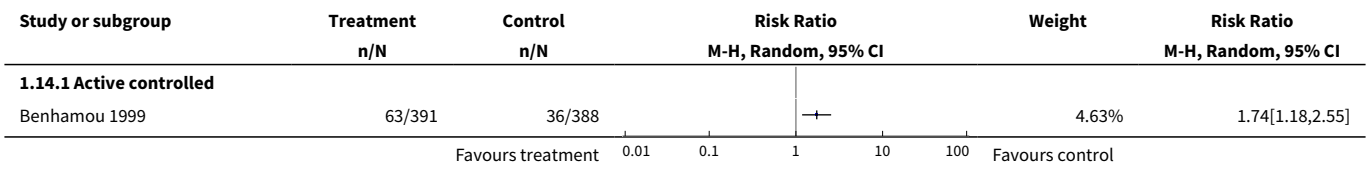


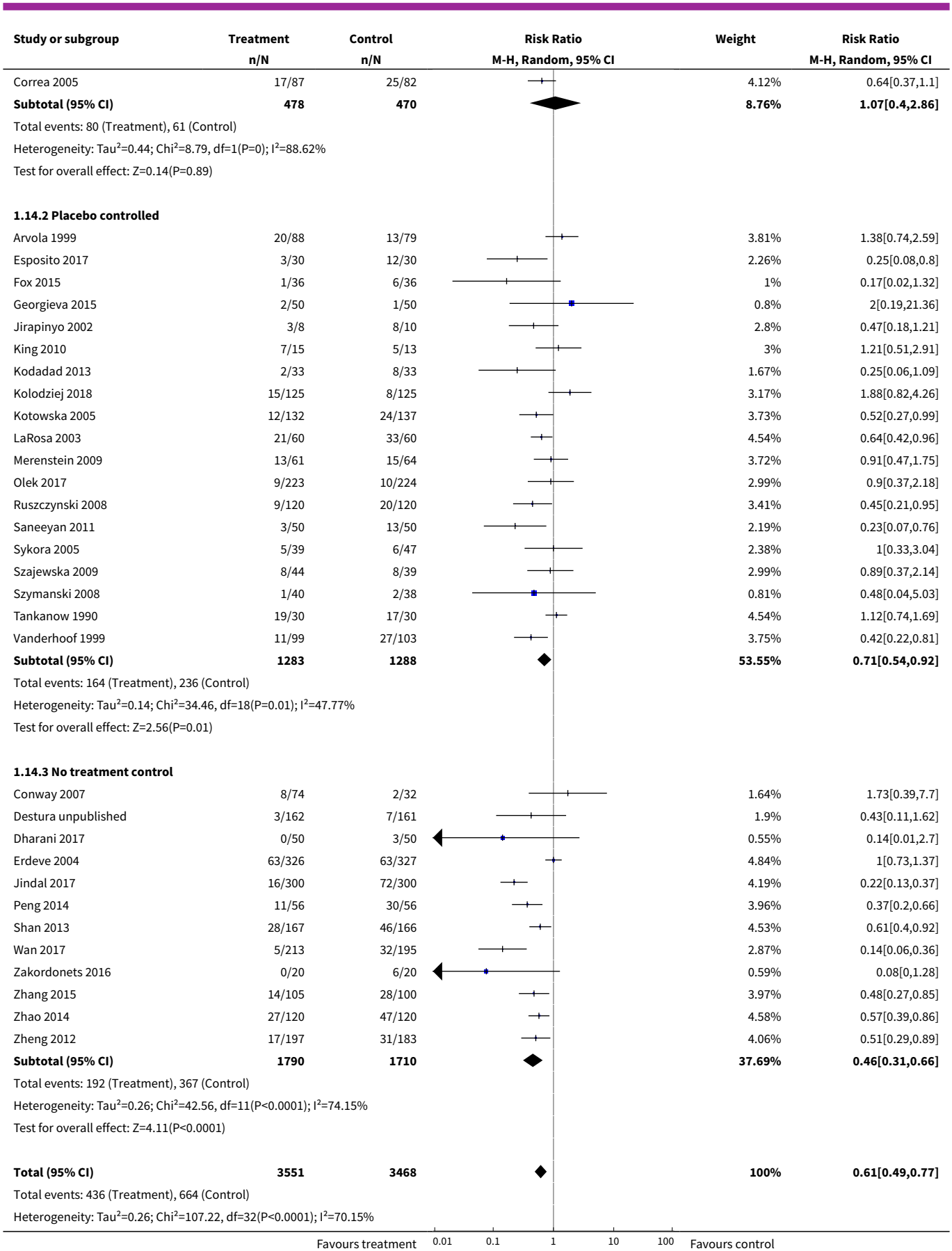
Analysis 1.13. Comparison 1 Probiotics versus control, Outcome 13 Incidence of diarrhea: Probiotic dose (extreme-plausible analysis).

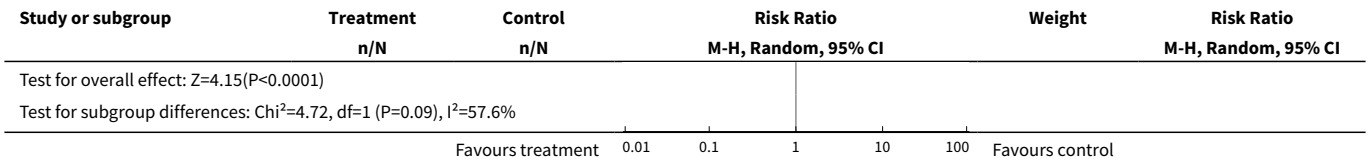




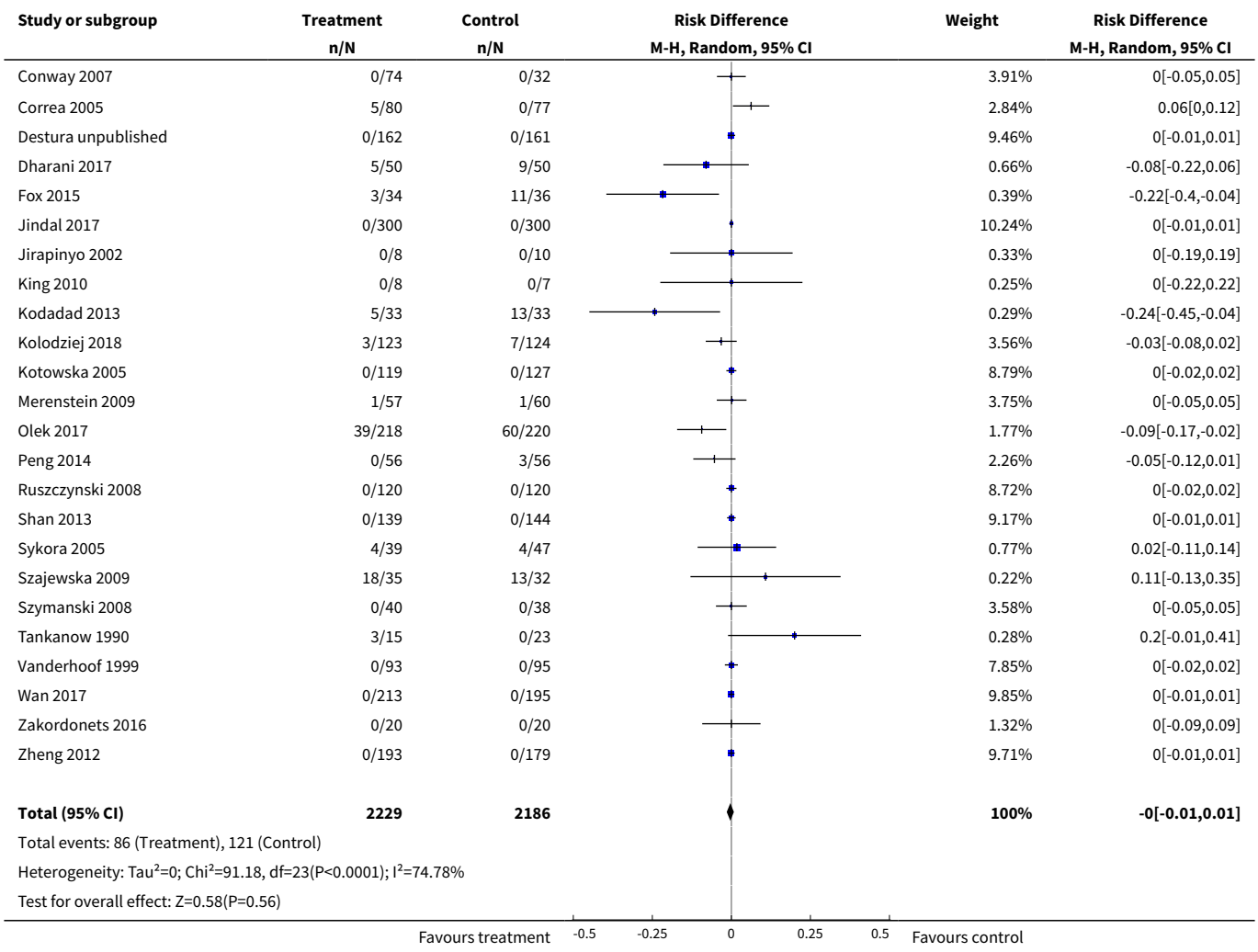
Analysis 1.14. Comparison 1 Probiotics versus control, Outcome 14 Incidence of diarrhea: Sensitivity analysis (missing outcome data - extreme plausible analysis).



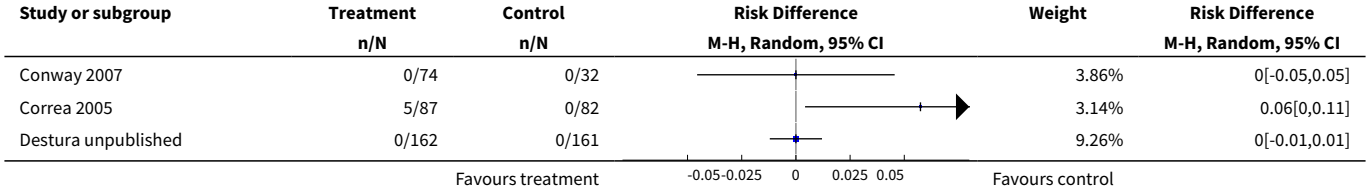


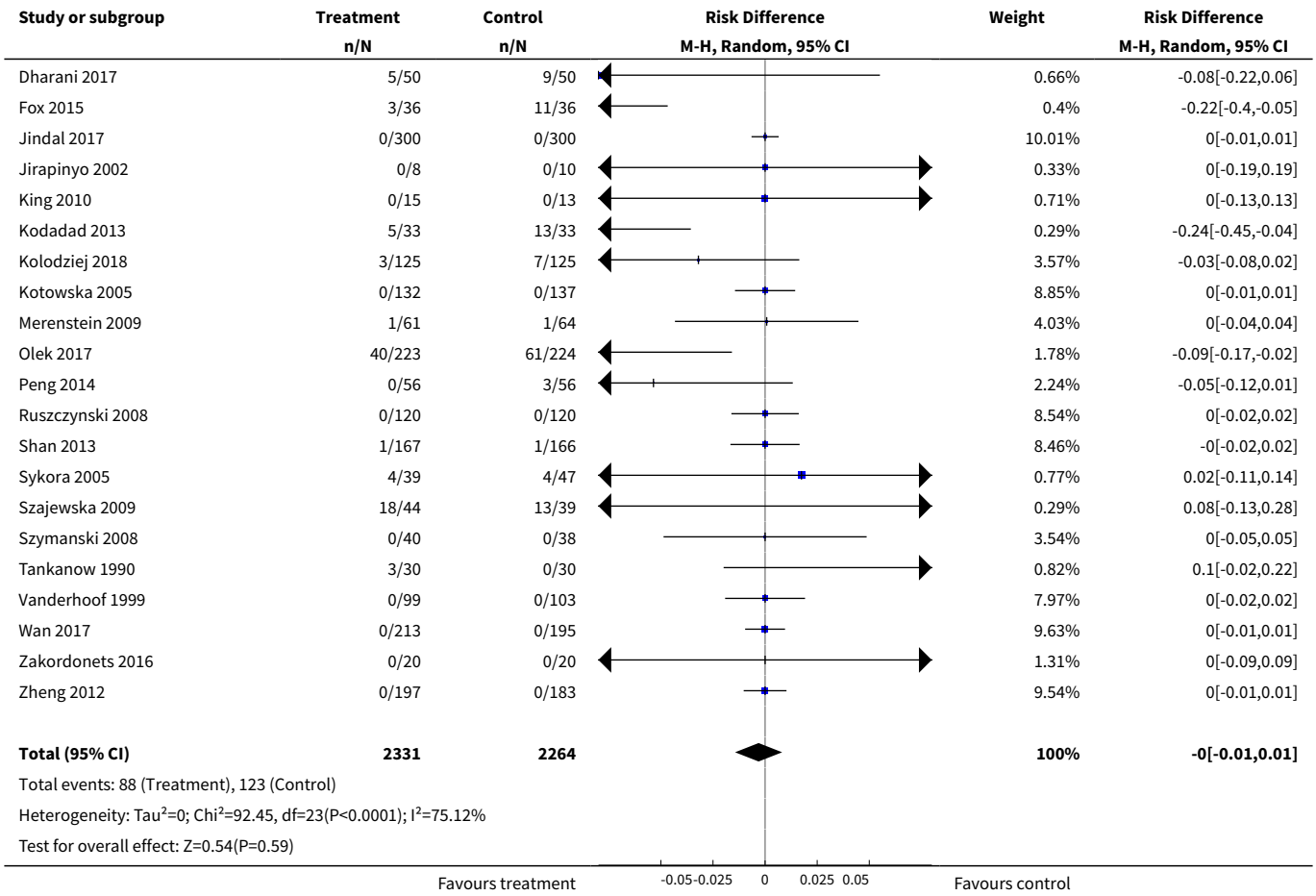


Analysis 1.15. Comparison 1 Probiotics versus control, Outcome 15 Adverse events: Complete case.

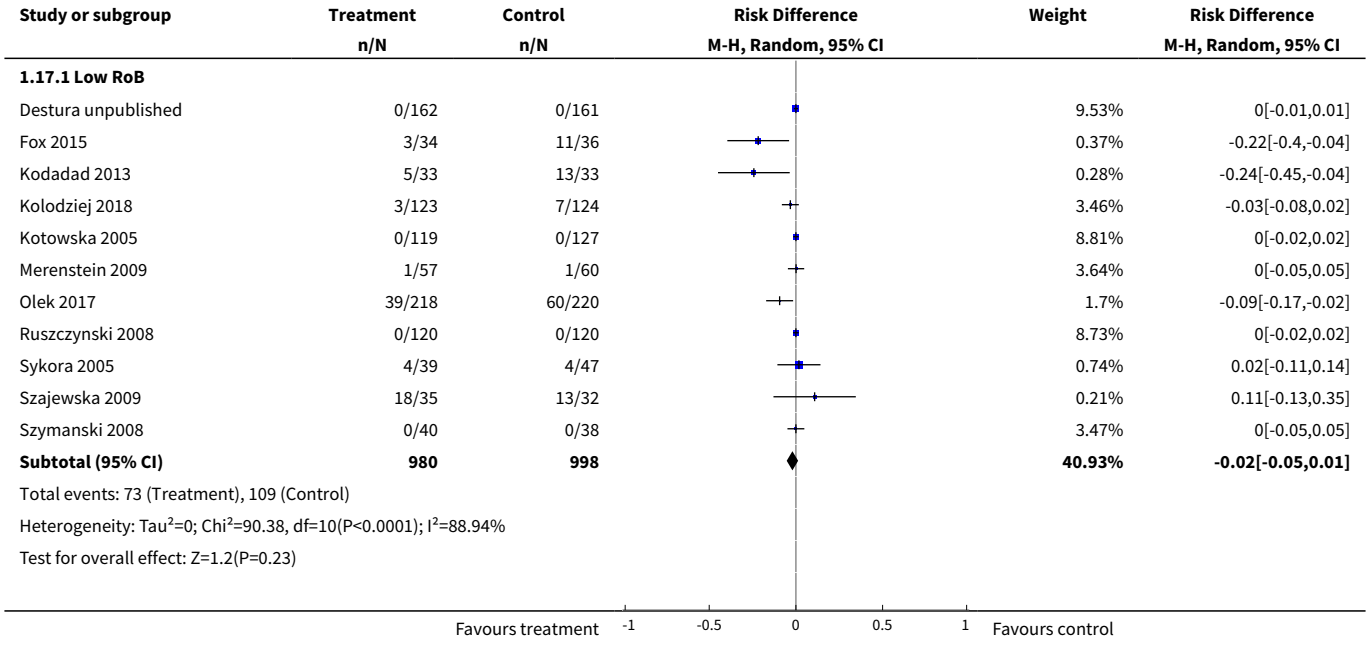


Analysis 1.16. Comparison 1 Probiotics versus control, Outcome 16 Adverse events: Same event rate assumptions analysis.

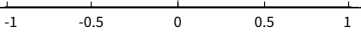




Analysis 1.17. Comparison 1 Probiotics versus control, Outcome 17 Adverse events: Risk of bias.

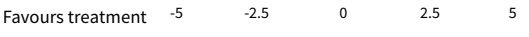


Study or subgroup	Treatment n/N	Control n/N	Risk Difference M-H, Random, 95% CI	Weight	Risk Difference M-H, Random, 95% CI
1.17.2 High/Unclear					
Conway 2007	0/74	0/32		3.8%	0[-0.05,0.05]
Correa 2005	5/80	0/77		2.74%	0.06[0,0.12]
Dharani 2017	5/50	9/50		0.63%	-0.08[-0.22,0.06]
Jindal 2017	0/300	0/300		10.36%	0[-0.01,0.01]
Jirapinyo 2002	0/8	0/10		0.32%	0[-0.19,0.19]
King 2010	0/8	0/7		0.24%	0[-0.22,0.22]
Peng 2014	0/56	2/56		2.68%	-0.04[-0.09,0.02]
Shan 2013	0/139	0/144		9.21%	0[-0.01,0.01]
Tankanow 1990	3/15	0/23		0.27%	0.2[-0.01,0.41]
Vanderhoof 1999	0/93	0/95		7.82%	0[-0.02,0.02]
Wan 2017	0/213	0/195		9.94%	0[-0.01,0.01]
Zakordonets 2016	0/20	0/20		1.26%	0[-0.09,0.09]
Zheng 2012	0/193	0/179		9.8%	0[-0.01,0.01]
Subtotal (95% CI)	**1249**	**1188**		**59.07%**	**0[-0,0]**
Total events: 13 (Treatment), 11 (Control)					
Heterogeneity: Tau^2=0; Chi^2=11.53, df=12(P=0.48); I^2=0%					
Test for overall effect: Z=0.07(P=0.94)					
Total (95% CI)	**2229**	**2186**		**100%**	**-0[-0.01,0.01]**
Total events: 86 (Treatment), 120 (Control)					
Heterogeneity: Tau^2=0; Chi^2=86.81, df=23(P<0.0001); I^2=73.5%					
Test for overall effect: Z=0.53(P=0.59)					
Test for subgroup differences: Chi^2=1.43, df=1 (P=0.23), I^2=29.97%					



Analysis 1.18. Comparison 1 Probiotics versus control, Outcome 18 Mean duration of diarrhea: Complete case.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Arvola 1999	60	4 (1.5)	59	4 (1.5)		12.93%	0[-0.54,0.54]
Correa 2005	80	3.9 (2.5)	77	5 (2.8)		10.51%	-1.08[-1.91,-0.25]
Destura unpublished	162	4 (3.5)	161	3.9 (2.3)		12.12%	0.14[-0.5,0.78]
Esposito 2017	30	1.5 (1.5)	30	2.8 (1.6)		10.86%	-1.3[-2.08,-0.52]
LaRosa 2003	56	0.7 (1.4)	54	1.6 (2)		12.03%	-0.9[-1.55,-0.25]
Peng 2014	56	3.2 (1.2)	56	5.3 (1.6)		13.06%	-2.1[-2.62,-1.58]
Vanderhoof 1999	93	4.7 (1.5)	95	5.9 (1.6)		13.69%	-1.18[-1.62,-0.74]
Zhang 2015	102	3.2 (1.1)	92	4 (0.9)		14.8%	-0.85[-1.12,-0.58]
Total ***	**639**		**624**			**100%**	**-0.91[-1.38,-0.44]**
Heterogeneity: Tau^2=0.37; Chi^2=43.93, df=7(P<0.0001); I^2=84.07%							
Test for overall effect: Z=3.79(P=0)							



APPENDICES

Appendix 1. Search strategies

MEDLINE

1 exp probiotics/ or probiotic*.mp.

2 exp lactobacillus/ or (lactobacill* or "l acidophilus" or "l casei").mp.

3 exp bifidobacterium/ or (bifidobacter* or "b infantis" or "b bifidum" or "b longum").mp.

4 exp saccharomyces/ or (saccaromyce* or "s boulardii").mp.

5 clostridium butyricum/ or clostridium difficile/ or (clostridium butyricum or clostridium difficile).mp.

6 streptococcus thermophilus/ or streptococcus thermophilus.mp.

7 enterococcus faecium/ or enterococcus faecium.mp.

8 or/1-7

9 exp anti-bacterial agents/

10 (antibiotic* or anti biotic* or antimicrobial* or anti microbial* or antimycobial* or anti mycobial* or antimycobacteri* or anti mycobacteri* or antibacteri* or anti bacteri* or bacteriocid* or antiinfective* or anti infective*).mp.

11 or/9-10

12 exp diarrhea/ or (diarrhe* or diarrhoe* or diarhe* or diarhoe*).mp.

13 exp dysentery/ or dysenter*.mp.

14 gastroenteritis/ or (gastroenteritis or gastro enteritis).mp.

15 or/12-14

16 8 and 11 and 15

17 pediatrics/

18 (infan* or newborn* or new-born* or perinat* or neonat* or baby or baby* or babies or toddler* or minors or minors* or boy or boys or boyfriend or boyhood or girl* or kid or kids or child or child* or children* or schoolchild* or schoolchild or adolescen* or juvenil* or youth* or teen* or underage* or pubescen* or pediatric* or paediatric* or peadiatric* or prematur* or preterm*).mp.

19 school*.ti,ab.

20 or/17-19

21 16 and 20

22 randomized controlled trial.pt.

23 controlled clinical trial.pt.

24 randomized.ab.

25 placebo.ab.

26 drug therapy.fs.

27 randomly.ab.

28 trial.ab.

29 groups.ab.

30 or/21-29

31 exp animals/ not humans.sh.

32 30 not 31

33 21 and 32

Embase

1 'probiotic agent'/exp OR probiotic*

2 'lactobacillus'/exp OR lactobacill* OR 'l acidophilus' OR 'l casei'

3 'bifidobacterium'/exp OR bifidobacter* OR 'b infantis' OR 'b bifidum' OR 'b longum'

4 'saccharomyces'/exp OR saccaromyce* OR 's boulardii'

5 'clostridium butyricum'/exp OR 'peptoclostridium difficile'/exp OR 'clostridium butyricum' OR 'clostridium difficile' OR 'peptoclostridium difficile'

6 'streptococcus thermophilus'/exp OR 'streptococcus thermophilus'

7 'enterococcus faecium'/exp OR 'enterococcus faecium'

8 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7

9 'antiinfective agent'/exp

10 antibiotic* OR 'anti biotic*' OR antimicrobial* OR 'anti microbial*' OR antimycobial* OR 'anti mycobial*' OR antimycobacteri* OR 'anti mycobacteri*' OR antibacteri* OR 'anti bacteri*' OR bacteriocid* OR antiinfective* OR 'anti infective*'

11 #9 OR #10

12 diarrhea'/exp OR diarrhe* OR diarrhoe* OR diarhe* OR diarhoe*

13 'dysentery'/exp OR dysenter*

14 'gastroenteritis'/exp OR gastroenteritis OR 'gastro enteritis'

15 #12 OR #13 OR #14

16 #8 AND #11 AND #15

17 'pediatrics'/de

18 infan* OR newborn* OR 'new-born*' OR perinat* OR neonat* OR baby OR baby* OR babies OR toddler* OR minors OR minors* OR boy OR boys OR boyfriend OR boyhood OR girl* OR kid OR kids OR child OR child* OR children* OR schoolchild* OR schoolchild OR adolescen* OR juvenil* OR youth* OR teen* OR underage* OR pubescen* OR pediatric* OR paediatric* OR peadiatric* OR prematur* OR preterm*

19 school*:ti,ab

20 #17 OR #18 OR #19

21 #16 AND #20

22 random*

23 'clinical trial*'

24 'treatment outcome'/exp

25 #22 OR #23 OR #24

26 'human'/de

27 'nonhuman'/de

28 'animal'/exp

29 'animal experiment'/de

30 #27 OR #28 OR #29

31 #30 NOT #26

32 #25 NOT #31

33 #21 AND #32

CENTRAL

1 probiotic*

2 lactobacill* or "l acidophilus" or "l casei"

3 bifidobacter* or "b infantis" or "b bifidum" or "b longum"

4 saccaromyce* or "s boulardii"

5 clostridium butyricum or clostridium difficile

6 streptococcus thermophilus

7 enterococcus faecium

8 #1 or #2 or #3 or #4 or #5 or #6 or #7

9 antibiotic* or anti biotic* or antimicrobial* or anti microbial* or antimycobial* or anti mycobial* or antimycobacteri* or anti mycobacteri* or antibacteri* or anti bacteri* or bacteriocid* or antiinfective* or anti infective*

10 diarrhe* or diarrhoe* or diarhe* or diarhoe*

11 dysenter*

12 gastroenteritis or gastro enteritis

13 #10 or #11 or #12

14 #8 and #9 and #13

15 infan* or newborn* or 'new-born*' or perinat* or neonat* or baby or baby* or babies or toddler* or minors or minors* or boy or boys or boyfriend or boyhood or girl* or kid or kids or child or child* or children* or schoolchild* or schoolchild or adolescen* or juvenil* or youth* or teen* or underage* or pubescen* or pediatric* or paediatric* or peadiatric* or prematur* or preterm*

16 school*:ti,ab

17 #15 or #16

18 #14 and #17

CINAHL with Full Text

1 (MH "Probiotics") OR probiotic*

2 (MH "Lactobacillus+") OR lactobacill* OR "l acidophilus" OR "l casei"

3 (MH "Bifidobacterium") OR bifidobacter* OR "b infantis" OR "b bifidum" OR "b longum"

4 (MH "Saccharomyces") OR saccaromyce* OR "s boulardii"

5 (MH "Clostridium Difficile") OR clostridium butyricum OR clostridium difficile

6 streptococcus thermophilus

7 (MH "Enterococcus Faecium") OR enterococcus faecium

8 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7

9 (MH "Antiinfective Agents+")

10 antibiotic* OR anti biotic* OR antimicrobial* OR anti microbial* OR antimycobial* OR anti mycobial* OR antimycobacteri* OR anti mycobacteri* OR antibacteri* OR anti bacteri* OR bacteriocid* OR antiinfective* OR anti infective*

11 S9 OR S10

12 (MH "Diarrhea") OR diarrhe* OR diarrhoe* OR diarhe* OR diarhoe*

13 (MH "Dysentery+") OR dysenter*

14 (MH "Gastroenteritis") OR gastroenteritis OR gastro enteritis

15 S12 OR S13 OR S14

16 S8 AND S11 AND S15

17 (MH "Pediatrics")

18 infan* OR newborn* OR new-born* OR perinat* OR neonat* OR baby OR baby* OR babies OR toddler* OR minors OR minors* OR boy OR boys OR boyfriend OR boyhood OR girl* OR kid OR kids OR child OR child* OR children* OR schoolchild* OR schoolchild OR adolescen* OR juvenil* OR youth* OR teen* OR underage* OR pubescen* OR pediatric* OR paediatric* OR peadiatric* OR prematur* OR preterm*

19 TI school* OR AB school*

20 S17 OR S18 OR S19

21 S16 AND S20

22 (MH "Treatment Outcomes+")

23 experimental studies

24 TX random*

25 S22 OR S23 OR S24

26 S21 AND S25

Web of Science Core Collection

1 TS=probiotic*

2 TS=(lactobacill* OR "l acidophilus" OR "l casei")

3 TS=(bifidobacter* OR "b infantis" OR "b bifidum" OR "b longum")

4 TS=(saccaromyce* OR "s boulardii")

5 TS=("clostridium butyricum" OR "clostridium difficile")

6 TS="streptococcus thermophilus"

7 TS="enterococcus faecium"

8 #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1

9 TS=(antibiotic* OR "anti biotic*" OR antimicrobial* OR "anti microbial*" OR antimycobial* OR "anti mycobial*" OR antimycobacteri* OR "anti mycobacteri*" OR antibacteri* OR "anti bacteri*" OR bacteriocid* OR antiinfective* OR "anti infective*")

10 TS=(diarrhe* OR diarrhoe* OR diarhe* OR diarhoe*)

11 TS=dysenter*

12 TS=(gastroenteritis OR "gastro enteritis")

13 #12 OR #11 OR #10

14 #13 AND #9 AND #8

15 TS=(infan* OR newborn* OR "new-born*" OR perinat* OR neonat* OR baby OR baby* OR babies OR toddler* OR minors OR minors* OR boy OR boys OR boyfriend OR boyhood OR girl* OR kid OR kids OR child OR child* OR children* OR school* OR adolescen* OR juvenil* OR youth* OR teen* OR underage* OR pubescen* OR pediatric* OR paediatric* OR peadiatric* OR prematur* OR preterm*)

16 #15 AND #14

17 TS=("clinical trial*" OR "research design" OR "comparative stud*" OR "evaluation stud*" OR "controlled trial*" OR "follow-up stud*" OR "prospective stud*" OR random* OR placebo* OR "single blind*" OR "double blind*")

18 TS=animal* NOT TS=human*

19 #17 NOT #18

20 #19 AND #16

Appendix 2. Assessing the credibility of a subgroup analysis results: 5 questions*

Table 1. Are the subgroup results significant?

Analysis number and name of subgroup	Number of studies	P value	Y/N (Is it significant?)
1.2 IOD: Inpatient vs outpatient	21	0.12	N
1.3 IOD: Diagnosis	27	0.91	N
1.4 IOD: Probiotic species**	15[1]	0.94	N
1.5 IOD: Single strain vs multi strain	33	0.34	N
1.6 IOD: Probiotic dose	32	0.01	Y
1.7 IOD: Definition of diarrhea**	22[2]	0.30	N
1.8 IOD: Strictness of definition	25	0.95	N
1.9 IOD: Industry sponsorship	17	0.52	N
1.10 IOD: Risk of bias	33	0.30	N
1.11 IOD: Age	32	0.18	N

Footnote:

* Sun X, Ioannidis JP, Agoritsas T, Alba AC, Guyatt G. How to use a subgroup analysis: users' guide to the medical literature. JAMA. 2014 Jan 22-29;311(4):405-11.

** We added an extra subgroup criterion based on number of studies for subgroups of interest; to do so we deleted those subgroups which included less than 5 studies (e.g. species and strain often have subgroup estimates for 1 to 4 studies. Otherwise, observed subgroup effects may underpowered and may be due to between study variability (age, socioeconomic status) that correlate with the outcome of interest.

[1] Studies included the species which named “Lactobacillus rhamnosus (strain: GG and E/N, Oxy, Pen)” and “*Saccharomyces boulardii*” and there are 6 and 9 studies, respectively.

[2] Studies include 2 definitions of AAD: “3 or more loose/watery/liquid stools per day for at least 2 consecutive days” and “3 or more watery/liquid stools per 24 hours” with 13 and 9 studies, respectively, falling into these categories.

Table 2. the credibility of the subgroup analysis of "Probiotic dose"

Items of subgroup	Answer
1. Based P-value Above, Can Chance Explain the Subgroup Difference?	Probably No (P = 0.008)
2. Is the Subgroup Difference Consistent Across Studies?	Probably Yes. High does studies mostly tend to have larger treatment effects. Results not driven by large studies
3. Was the Subgroup Difference One of a Small Number of a Priori Hypotheses in Which the Direction Was Accurately Prespecified?	Probably Yes. We tested 9 a priori subgroups
4. Is There a Strong Preexisting Biological Rationale Supporting the Apparent Subgroup Effect?	Probably Yes. Previous studies have demonstrated a dose response (see citations in review). However, dose may be confounded by studies that use multiple strains which may increase effectiveness
5. Is the Subgroup Difference Suggested by Comparisons within Rather than Between Studies?	No. The observed dose-response difference among all 33 studies is based on between study data.

* Given this, the dose response is unlikely attributable to within-study rather than between study differences.

WHAT'S NEW

Date	Event	Description
13 May 2019	Amended	Correction of minor error in plain language summary

HISTORY

Protocol first published: Issue 3, 2004
Review first published: Issue 2, 2007

Date	Event	Description
28 May 2018	New citation required but conclusions have not changed	Updated review with new authors
28 May 2018	New search has been performed	New search, new studies added

CONTRIBUTIONS OF AUTHORS

This version of the review:

Qin Guo: Screening, inclusion/exclusion, data extraction, quality assessment, data analysis, manuscript preparation, administrative and technical support.

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

Claire Humphrey: Data extraction, quality assessment, manuscript preparation.

Regina El Dib: Screening, data interpretation, 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, 2011 and 2015 versions of the Cochrane review for previous contributions (Johnston 2007; Johnston 2011; Goldenberg 2015).

DECLARATIONS OF INTEREST

Qin Guo: None known.

Joshua Z Goldenberg: None known.

Claire Humphrey: None known.

Regina El Dib: None known.

Bradley C Johnston: None known.

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

1. In our previous 2015 review, we abstracted data on mean stool frequency and mean stool consistency. Since there were very limited data available on these outcomes (i.e. only 4 studies reported stool frequency, none reported stool consistency independently) and given that this outcome overlaps with AAD (a more patient important outcome), we have removed these outcomes. In this update review, we have included microbiome characteristics as an outcome given the clinical communities interest in the impact of antibiotics and probiotics on the microbiome.

2. In our previous 2015 review, we assessed the effectiveness of probiotics for AAD prevention based on the definition of diarrhea using two subgroups: 1. strictness of definition, 2. definition of diarrhea. For 'strictness of diarrhea', we previously used two categories '> or = to moderate' versus '< moderate'. For this update, we have revised the wording to 'moderate' versus 'mild' AAD.

3. In our previous 2015 review, we referred to diagnosis, inpatient versus outpatient, single versus multiple species and industry sponsorship as post hoc subgroup analyses as these were generated based on peer-review feedback. In this update review, we have considered each of these as a priori subgroups. We now have nine a priori subgroups in total.

4. Based on prospective observational data that provides the best estimate of the baseline risk of AAD in children, in this review we have added one new post-hoc subgroup on age $\leq$ 24 months versus > 24 months.

NOTES

To assess risk of bias for blinding and to generate Figure 3, we collapsed both blinding domains (participants/personnel and outcome assessors). If both domains were low risk of bias, the risk of bias for blinding was low. If one domain was high and one low, we assumed risk of bias for blinding was high overall. If one domain was low and one unclear, we assumed risk of bias for blinding was low overall.

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Bacterial Agents [*adverse effects] [therapeutic use]; Diarrhea [etiology] [*prevention & control]; Probiotics [*therapeutic use]; Treatment Outcome

MeSH check words

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