Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children (Review)

Goldenberg JZ, Ma SSY, Saxton JD, Martzen MR, Vandvik PO, Thorlund K, Guyatt GH, Johnston BC

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[Intervention Review]

Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children

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ABSTRACT

Background

Antibiotics are widely prescribed; however they can cause disturbances in gastrointestinal flora which may lead to reduced resistance to pathogens such as *Clostridium difficile* (*C. difficile)*. Probiotics are live organisms thought to balance the gastrointestinal flora.

Objectives

The primary objectives were to assess the efficacy and safety of probiotics for preventing *Clostridium difficile*-associated diarrhea (CDAD) or *C. difficile* infection in adults and children.

Search methods

On February 21, 2013 we searched PubMed (1966-2013), EMBASE (1966-2013), Cochrane Central Register of Controlled Trials (*The Cochrane Library* 2013, Issue 1), CINAHL (1982-2013), AMED (1985-2013), and ISI Web of Science. Additionally, we conducted an extensive grey literature search including contact with industry representatives.

Selection criteria

Randomized controlled (placebo, alternative prophylaxis, or no treatment control) trials investigating probiotics (any strain, any dose) for prevention of CDAD, or *C. difficile* infection were considered for inclusion.

Data collection and analysis

Two authors independently and in duplicate extracted data and assessed risk of bias using pre-constructed, and piloted, data extraction forms. Any disagreements were resolved by a third adjudicator. For articles published in abstract form only, further information was sought by contacting principal authors. The primary outcome was the incidence of CDAD. Secondary outcomes included the incidence of *C. difficile* infection, adverse events, antibiotic-associated diarrhea (AAD) and length of hospital stay. Dichotomous outcomes (e.g. incidence of CDAD) were pooled using a random-effects model to calculate the relative risk and corresponding 95% confidence interval (95% CI). Continuous outcomes (e.g. length of hospital) were pooled using a random-effects model to calculate the mean difference

and corresponding 95% CI. Sensitivity analyses were conducted to explore the impact of missing data on efficacy and safety outcomes. For the sensitivity analyses, we assumed that the event rate for those participants in the control group who had missing data was the same as the event rate for those participants in the control group who were successfully followed. For the probiotic group we calculated effects using the following assumed ratios of event rates in those with missing data in comparison to those successfully followed: 1.5:1, 2:1, 3:1, and 5:1. To explore possible explanations for heterogeneity, *a priori* subgroup analysis were conducted on probiotic species, dose, adult versus pediatric population, and risk of bias.The overall quality of the evidence supporting each outcome was assessed using the GRADE criteria.

Main results

A total of 1871 studies were identified with 31 (4492 participants) meeting eligibility requirements for our review. Overall 11 studies were rated as a high risk of bias due mostly to missing outcome data. A complete case analysis (i.e. participants who completed the study) of those trials investigating CDAD (23 trials, 4213 participants) suggests that probiotics significantly reduce this risk by 64%. The incidence of CDAD was 2.0% in the probiotic group compared to 5.5% in the placebo or no treatment control group (RR 0.36; 95% CI 0.26 to 0.51). Sixteen of 23 trials had missing CDAD data ranging from 5% to 45%. These results proved robust to sensitivity analyses of plausible and worst-plausible assumptions regarding missing outcome data and were similar whether considering trials in adults versus children, lower versus higher doses, different probiotic species, or higher versus lower risk of bias. Our judgment is that the overall evidence warrants moderate confidence in this large relative risk reduction. We downgraded the overall quality of evidence for CDAD to 'moderate' due to imprecision. There were few events (154) and the calculated optimal information size (n = 8218) was more than the total sample size. With respect to the incidence of *C. difficile* infection, a secondary outcome, pooled complete case results from 13 trials (961 participants) did not show a statistically significant reduction. The incidence of *C. difficile* infection was 12.6% in the probiotics group compared to 12.7% in the placebo or no treatment control group (RR 0.89; 95% CI 0.64 to 1.24). Adverse events were assessed in 26 studies (3964 participants) and our pooled complete case analysis indicates probiotics reduce the risk of adverse events by 20% (RR 0.80; 95% CI 0.68 to 0.95). In both treatment and control groups the most common adverse events included abdominal cramping, nausea, fever, soft stools, flatulence, and taste disturbance. For the short-term use of probiotics in patients that are not immunocompromised or severely debilitated, we consider the strength of this evidence to be moderate.

Authors' conclusions

Based on this systematic review and meta-analysis of 23 randomized controlled trials including 4213 patients, moderate quality evidence suggests that probiotics are both safe and effective for preventing *Clostridium difficile*-associated diarrhea.

PLAIN LANGUAGE SUMMARY

The use of probiotics to prevent *C. difficile* diarrhea associated with antibiotic use

Antibiotics are among the most prescribed medications worldwide. Antibiotic treatment may disturb the balance of organisms that normally inhabit the gut. This can result in a range of symptoms, most notably, diarrhea. *Clostridium difficile* is one particularly dangerous organism that may colonize the gut if the normal healthy balance has been disturbed. *Clostridium difficile*-related disease varies from asymptomatic infection, diarrhea, colitis, and pseudo-membranous colitis to death. The cost of treatment is expensive and the financial burden on the medical system is substantial.

Probiotics are organisms thought to improve the balance of organisms that inhabit the gut, counteract disturbances to this balance, and reduce the risk of colonization by pathogenic bacteria. They are becoming increasingly available as capsules and food supplements sold in health food stores and supermarkets. As "functional food" or "good bacteria", probiotics have been suggested as a means of both preventing and treating *C. difficile*-associated diarrhea (CDAD).

This review includes 31 randomized trials with a total of 4492 participants. Twenty-three studies (4213 participants) assessed the effectiveness of probiotics in preventing CDAD in participants taking antibiotics. Our results suggest that when probiotics are given with antibiotics they reduce the risk of developing CDAD by 64%. Side effects were assessed in 26 studies (3964 participants) and our results suggest that probiotics decrease the risk of developing side effects. The most common side effects reported in these studies include abdominal cramping, nausea, fever, soft stools, flatulence, and taste disturbance. The short-term use of probiotics appears to be safe and effective when used along with antibiotics in patients who are not immunocompromised or severely debilitated.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Probiotics for the prevention of Clostridium difficile associated diarrhea

Patient or population: adults and children exposed to antibiotics
Settings: inpatient and outpatient
Intervention: probiotics

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Probiotics				
Clostridium difficile associated diarrhea diarrhea as defined by authors + cytotoxin and culture or both	**Study population**		**RR 0.36** (0.26 to 0.51)	4213 (23 studies)	⊕⊕⊕◯ **moderate**[1,2,3,4,5,6]	
	55 per 1000	**20 per 1000** (14 to 28)				
	Median					
	35 per 1000	**13 per 1000** (9 to 18)				
Adverse events as defined or described by authors	**Study population**		**RR 0.80** (0.68 to 0.95)	3964 (26 studies)	⊕⊕⊕◯ **moderate**[7,8,9,10,11]	
	187 per 1000	**150 per 1000** (127 to 178)				
	Median					
	69 per 1000	**55 per 1000** (47 to 66)				
Clostridium difficile infection cytotoxin and/or culture	**Study population**		**RR 0.89** (0.64 to 1.24)	961 (13 studies)	⊕⊕⊕◯ **moderate**[12,13,14,15,16]	

	127 per 1000	**113 per 1000** (82 to 158)			
	Median				
	105 per 1000	**93 per 1000** (67 to 130)			
Length of hospital stay days spent in hospital	The mean length of hospital stay in the control groups was **10.3 days**	The mean length of hospital stay in the intervention groups was **0.32 lower** (3.21 lower to 2.57 higher)		422 (3 studies)	⊕⊕◯◯ **low**[17,18,19,20,21]
Antibiotic associated diarrhea as defined by study authors	**Study population**		**RR 0.60** (0.49 to 0.72)	4097 (25 studies)	⊕⊕◯◯ **low**[22,23,24,25,26]
	209 per 1000	**125 per 1000** (102 to 151)			
	Median				
	220 per 1000	**132 per 1000** (108 to 158)			

*The basis for the **assumed 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; **RR:** Risk ratio;

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] Low risk of bias studies (7/23) demonstrated a slightly more favorable protective effect than studies at high or unclear risk of bias (16/23). A test for subgroup differences did not find a statistically significant difference based on risk of bias (P = 0.16).

[2] 16 of 23 trials had missing CDAD data ranging from 5 to 45%. A sensitivity analysis using plausible and worst-plausible ratios of event rates in those with missing data in comparison to those successfully followed, demonstrated the CDAD results were robust to all assumptions (worst-plausible analysis: RR 0.57; 95% CI 0.38 to 0.85).

[3] Effect sizes are consistent across all 23 studies (I^2 = 0%; P=0.76).

[4] Outcome assessed in all 23 studies is the outcome of interest for our health question.

[5] Using standard alpha (0.05) and beta (0.20) values, for a RRR of 30% the optimal information size (n = 8218) was more than the total sample size (n = 4213). Additionally, overall events were very low (154) and as a result we rated down for imprecision.

[6] Funnel plot inspection as well as Harbord's linear regression test (P = 0.11) are not suggestive of publication bias or other small study effects.

[7] Test for risk of bias subgroup differences was not statistically significant (P = 0.16). However, only 26 of 31 trials reported on adverse events, an outcome that would presumably be documented in all probiotics trials. We therefore rated down for selective reporting bias.

[8] Minimal heterogeneity between trials (I^2 = 37%; P = 0.06).

[9] Outcome assessed in these 26 studies is the outcome of interest for our health question.

[10] Using standard alpha (0.05) and beta (0.20) values, we calculated the optimal information size based on a relative risk decrease of 30%. The OIS (n = 4044) was greater than the total sample size (n = 3964). However, given that the number of overall events was high (events = 639) we did not rate down for imprecision.

[11] Funnel plot inspection and Harbord's linear regression test found no visual or statistical evidence of small study effects (P = 0.24).

[12] Three studies were rated as having a low risk of bias. Ten were rated as having an unclear or high risk of bias. A test for risk of bias subgroup differences was not statistically significant (P = 0.88).

[13] Effect sizes are consistent across the 13 studies reporting on *C. difficile* infection (I^2 = 0%; P = 0.84).

[14] Outcome assessed in all 13 studies is the outcome of interest for our health question.

[15] Total event rate of all 13 studies is very low (122) and the 95% confidence interval includes both no effect and a substantial effect size. We therefore rated down for imprecision.

[16] Funnel plot inspection as well as Harbord's linear regression test revealed no visual or statistical evidence of small study effects (P = 0.56).

[17] We suspect selective outcome reporting bias as only 3 of 31 identified trials, most of which occurred in hospitals, reported on length of hospital stay - a presumably patient and hospital important outcome. Of the three studies reporting on length of stay, one had an unclear risk of bias and two were rated as having a low risk of bias.

[18] Minimal heterogeneity between studies (I^2 = 20%; P = 0.29).

[19] Outcome assessed is the outcome of interest for our health question.

[20] Using an alpha of 0.05 and beta of 0.20, the optimal information size to detect a two day difference in hospital stay (n = 800) was larger than the pooled sample size (n = 422). We therefore rated down for imprecision.

[21] With only 3 trials reporting on length of stay, publication bias was not assessed.

[22] A test for subgroup differences between low risk of bias studies (n = 13) versus high risk or unclear risk of bias studies (n = 12) was not statistically significant (P = 0.74). Eleven of 25 trials had missing AAD data ranging from 4% to 43%. A sensitivity analysis using plausible and worst-plausible ratios of event rates in those with missing data in comparison to those successfully followed, demonstrated the AAD results were not robust to all assumptions (worst-plausible, RR 0.90; 95% CI 0.69 to 1.18). We therefore rated down for risk of bias associated with missing participant data.

[23] There was statistically significant heterogeneity across the 25 studies (I^2 = 36%. P = 0.04). We explored potential reasons for this observed heterogeneity using a priori defined subgroup analyses revealing that age (i.e. adult versus pediatric subgroup) may explain

the observed heterogeneity (test of interaction: P = 0.05). Using 11 published criteria to evaluate the credibility of this subgroup, our subgroup analysis on age represents a credible subgroup effect. We therefore did not rate down for inconsistency (Sun 2010).

[24] Outcome assessed in all 25 studies is the outcome of interest for our health question.

[25] Using an alpha of 0.05 and beta of 0.20, for a RRR of 30% the optimal information size (n = 1094) was less than the total sample size (n = 4097).

[26] While the funnel plot may suggest asymmetry, Harbord's linear regression test was negative for publication (or other small study effect) bias (P = 0.31). However our inclusion criteria (trials reporting on *C. difficile*) likely introduced a selection bias and we again rated down our confidence in the estimate of effect.

BACKGROUND

Antibiotics are among the most prescribed medications worldwide. Antibiotic treatment may disturb the colonization resistance of gastrointestinal flora, resulting in a range of symptoms, most notably, diarrhea. *Clostridium difficile* (*C. difficile*) is the pathogen most often associated with opportunistic proliferation after breakdown of colonization resistance due to antibiotic administration. The spectrum of *C. difficile*-related disease varies from asymptomatic intestinal colonization, diarrhea, colitis, and pseudo-membranous colitis to death (Berrington 2004). In the United States incremental cost estimates of *C. difficile* infection range from $2,871 to $4,846 per case for primary *C. difficile* infection and from $13,655 to $18,067 per case for recurrent infection (Ghantoji 2010).

Probiotics are live organisms thought to improve the microbial balance of the host, counteract disturbances in intestinal flora, and reduce the risk of colonization by pathogenic bacteria (Sullivan 2002). They are becoming increasingly available as capsules and dairy based food supplements sold in health food stores and supermarkets (Drisko 2005). As "functional food" or "good bacteria/yeast", probiotics have been suggested as a means of preventing *C. difficile*-associated diarrhea (CDAD) (D'Souza 2002; Dendukuri 2005). If effective, the low cost as well as the low incidence of adverse events (Hempel 2012) may make probiotics an attractive intervention to prevent *Clostridium difficile*-related disease.

We conducted a systematic review and meta-analysis to assess the efficacy and safety of probiotics for the prevention of CDAD in adults and children receiving antibiotics.

OBJECTIVES

The primary objectives were to assess the efficacy and safety of probiotics for the prevention of *C. difficile*-associated diarrhea in adults and children.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCT) reporting incidence outcomes for CDAD (diarrhea & positive stool cytotoxin/culture for *C. difficile*) or *C. difficile* infection (positive stool cytotoxin/culture for *C. difficile*) were considered for inclusion.

Types of participants

Participants included adult (> 18 years) and paediatric patients (0 to 18 years of age) receiving antibiotic therapy for any reason.

Types of interventions

The interventions of interest compared probiotics (any strain or dose) versus placebo, alternative prophylaxis, or no treatment for the prevention of *C. difficile*-associated diarrhea in adults and children receiving antibiotic therapy. Studies using probiotics for the treatment of *C. difficile* were excluded.

Types of outcome measures

The primary outcome was the incidence of *C. difficile*-associated diarrhea. Secondary outcomes included incidence of *C. difficile* infection, adverse events, antibiotic-associated diarrhea, and length of hospital stay.

Search methods for identification of studies

Electronic searches

On February 21, 2013, we performed a comprehensive search using the following electronic databases: PubMed (1966 to 2013), EMBASE (1966 to 2013), CENTRAL (2013, Issue 1), CINAHL (1982 to 2013), AMED (1985 to 2013), and ISI Web of Science (the first 500 citations of ISI's large retrieval set were prescreened). Searches included both controlled vocabulary (e.g. Probiotics, Cultured Milk Products) and text words (e.g. "fermented foods", gastroenteritis). No language, publication status, or date limits were applied. Each search strategy was adapted for the particular database. See Appendix 1 for the EMBASE search strategy.

Searching other resources

In addition, reference lists for relevant studies and systematic reviews were checked to make sure all cited RCTs had been identified in the electronic searches. BIOSIS (Thomson Reuters; 1969 to 2013) was searched specifically for conference proceedings as well as the British Society of Gastroenterology Annual General Meeting abstracts (years: 2006 to 2013) and Digestive Disease Week (years: 2009 to 2013). Authors of pertinent presentations were contacted for further information. The following sources were also reviewed: Canadian Agency for Drugs and Technologies in Health; McGill University Health Centre, Technology Assessment Unit; trial registers, e.g. the Inflammatory Bowel Disease and Functional Bowel Disorders Review Group's specialized trials register, and the metaRegister of Controlled Trials, dissertations abstracts (Proquest's Theses and Dissertations Full Text); TRIP Database; Highwire Press; and Google Scholar. To complete the search process, companies that manufacture probiotic agents

(Metagenics; Seroyal/Pharmax; Yeo Valley Organics; Biocodex Inc.; Sanofi-Aventis; Probugs/Lifeway Foods Inc.; IBSS Biomed S.A.) were contacted to identify any unpublished, ongoing, randomised trials.

Data collection and analysis

Selection of studies

Using pre-specified eligibility criteria, two authors independently screened titles and abstracts for potential full text eligibility. If reviewers deemed any title or abstract as potentially eligible, the articles were retrieved for full-text eligibility assessment. Two authors independently assessed the eligibility of each full-text article. Disagreement was resolved by consensus.

Data extraction and management

Two authors (SSYM, BCJ) independently extracted data on patients, methods, interventions, and outcomes, using a pre-constructed, standardized data extraction form. We extracted information on the number of patients allocated to each group, presence or absence of intention-to-treat analysis (whether patients for whom data were available were analyzed as randomized), and the number of participants with missing outcome data. If follow-up was incomplete, we extracted any reported reasons for missing data and information about methods of imputation. Disagreement was resolved by a third adjudicator (GHG). For articles published in abstract form only, further information was sought by contacting principal authors.

Risk of bias and quality assessment

Two reviewers independently assessed the risk of bias (JZG, POV) in the individual RCTs as described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). Risk of bias factors assessed were sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias (e.g. distribution of baseline characteristics, industry initiation and funding, study stopped early).

Statistical analysis

Statistical software used for data analysis included the RevMan Analyses statistical package in Review Manager (Review Manager 2012) and the statistical packages 'meta,' 'metafor,' 'rmeta' and 'extfunnel' within the statistical environment of R (R version 2.14.1) (Lumley 2009; R Development Core Team 2010; Schwarzer 2010; Viechtbauer 2010; Langan 2012). Using a random-effects model, dichotomous data were presented as a relative risk (RR) along with corresponding 95% confidence intervals (95% CI). The number needed to treat for an additional beneficial outcome (NNTB) or the number needed to treat for an additional harmful outcome (NNTH) were also calculated for each outcome as appropriate, as well as the absolute risk expressed as both a percentage and as natural units (See Summary of findings for the main comparison). For calculating natural units (risk per 1000 patients), the control group risk estimates come from the pooled estimate of the control arm of the meta-analysis.

Dealing with missing data

To explore the impact of missing outcome data on statistically significant efficacy results, we compared our primary analysis (i.e. a complete case analysis) to a series of sensitivity analyses. For the purposes of this systematic review missing outcome data can be understood as incomplete ascertainment of the primary outcome for some participants. Patients for whom data were not available for the primary outcome were classified as "missing". For the sensitivity analyses, we assumed that the event rate for those participants in the control group who had missing data was the same as the event rate for those participants in the control group who were successfully followed. For the probiotic group we calculated effects using the following assumed ratios of event rates in those with missing data in comparison to those successfully followed: 1.5:1, 2:1, 3:1, and 5:1 (Akl 2012). We then determined if the sensitivity results withstood the range of assumptions.

Assessment and investigation of heterogeneity

For our primary outcome, heterogeneity was investigated using the Chi^2 test and I squared statistic (Higgins 2003). To explore possible explanations for heterogeneity, the following subgroup analyses were planned *a priori*: probiotic species, with a larger effect expected in trials of *S. boulardii* or *L. rhamnosus* (Johnston 2011); dosage of probiotic, with an expected larger effect in trials administering an increased dose (Johnston 2006; Johnston 2011); adult versus pediatric population, with a postulated larger effect in adults for CDAD and children for AAD (Hempel 2012); and the risk of bias, with an expected larger effect in trials at high or unclear risk of bias versus trials at low risk of bias (Higgins 2011). *Post hoc*, on the recommendation of a peer reviewer we conducted a subgroup on inpatients versus outpatients, with a postulated larger effect among inpatients. To evaluate the credibility of our subgroup analyses we used pre-specified criteria, including a test for interaction (Sun 2010). For continuous variables such as probiotic dose, we used random-effects meta-regression (Thompson 2002).

Assessment of publication bias

To evaluate the potential for publication bias and other small study effects, we followed recently published guidelines and inspected the funnel plots of each outcome for visual evidence of asymmetry

and then conducted Harbord's linear regression test to investigate statistical evidence of small study effects (Harbord 2006; Sterne 2011).

Assessment of the impact of a future trial

By visualizing where in a funnel plot a future trial would have to lie to negate the statistical significance of the meta-analysis, graphical augmentations of a funnel plot may give an indication of the robustness of the meta-analysis (Langan 2012). We constructed graphical augmentations to our funnel plots in order to investigate the theoretical impact that any large future study might have on the statistical significance of our results.

Assessment of the quality of evidence

We rated the overall quality of evidence (i.e., confidence in effect-estimates) for each of the outcomes in the meta-analyses using the GRADE approach where randomised 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) inconsistency, (3) indirectness, (4) imprecision, and (5) reporting bias (Guyatt 2008). Rating of the overall quality of evidence for each outcome was done independently and in duplicate (BCJ, JZG) with disagreement resolved by consensus.

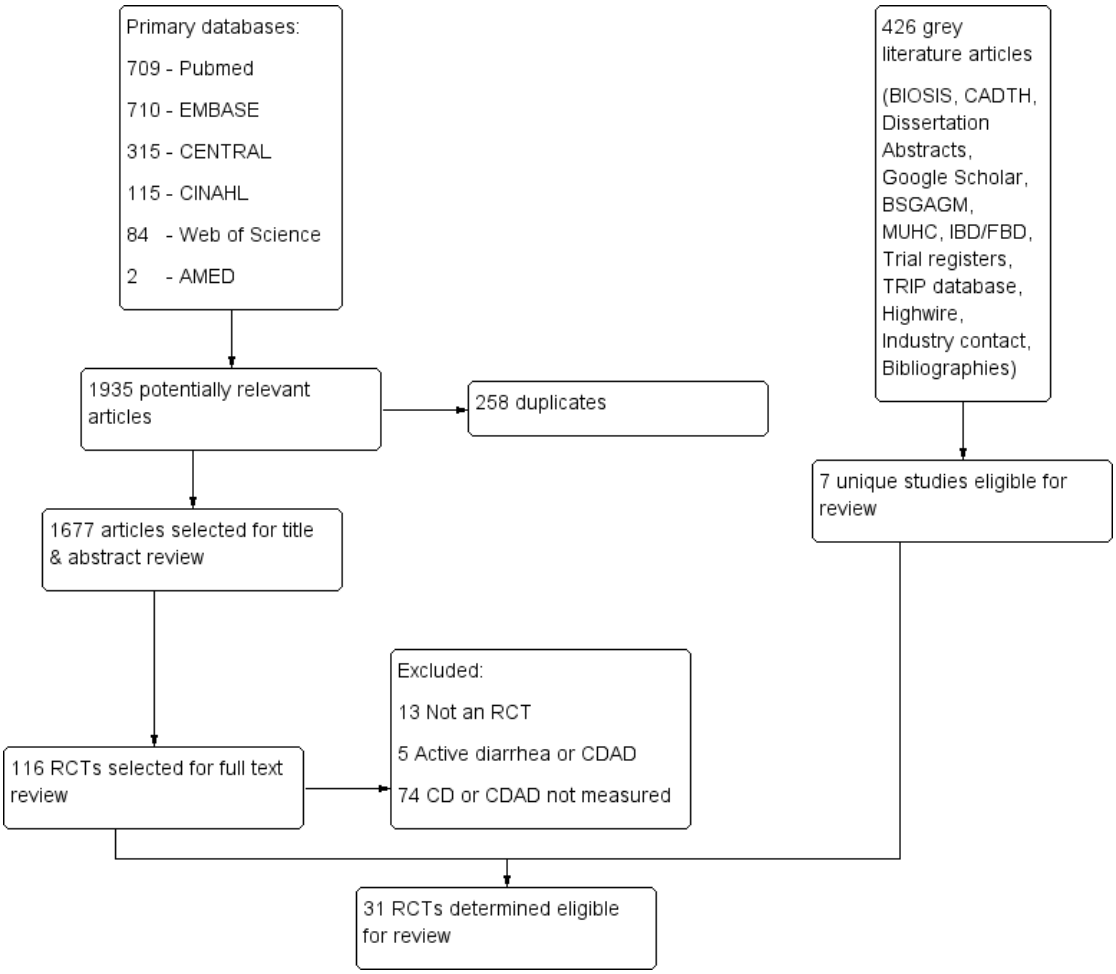
RESULTS

Description of studies

Results of the search

A total of 1935 studies were identified from the primary electronic databases (Pubmed 709, EMBASE 710, CENTRAL 315, CINAHL 115, Web of Science 84, AMED 2). Of these, 258 were identified as duplicates, leaving 1677 abstracts and titles identified as original publications. Of these, 116 studies were eligible for full text review, and of these, 24 RCTs met the eligibility criteria of this systematic review. A grey literature search of eleven additional sources (e.g. BIOSIS, Dissertation Abstracts, Google Scholar, metaRegister of controlled trials), a review of bibliographies of included studies, as well as contact with industry identified 426 articles, 9 of which were unique studies not identified in our primary database search. Seven of these studies met our eligibility criteria (Miller 2008a; Miller 2008b; Psaradellis 2010; Rafiq 2007; Selinger 2011; Pozzoni 2012; Cindoruk 2007). Thirty-one studies (4492 participants) were included in the review. Figure 1 summarizes the flow of studies.

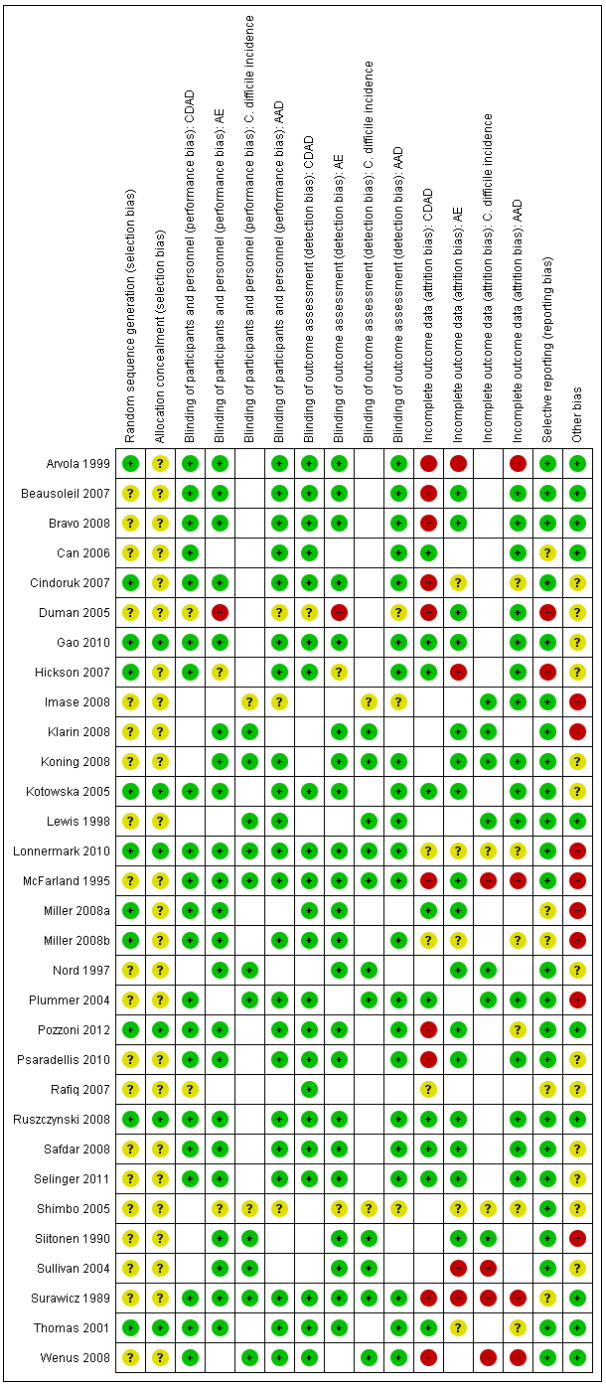
Figure 1. Flow of studies diagram.



Risk of bias in included studies

The risk of bias for each study was assessed for all outcomes as described in the Cochrane Handbook (Higgins 2011) and overall results are discussed with effects of interventions below. Figure 2 displays the risk of bias by domains and by study.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.Blanks cells indicate that this outcome was not assessed in the study.



Effects of interventions

See: **Summary of findings for the main comparison** Probiotics for the prevention of Clostridium difficile associated diarrhea

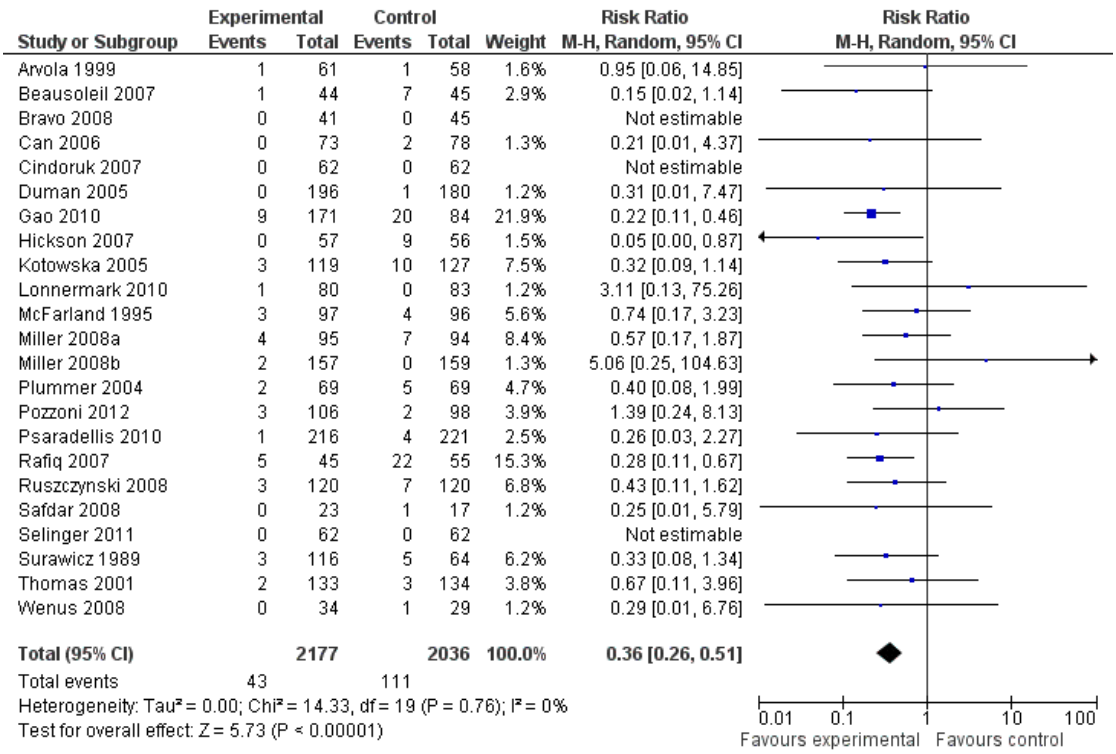
Outcomes

Incidence of *C. difficile*-associated diarrhea

To allow for a heterogeneous definition of CDAD, data (as a binary outcome) were included based on the primary authors' definition of the presence or absence of CDAD. Twenty-three studies (n = 4213) reported on the incidence of CDAD. Of these, 21 were placebo-controlled, one trial provided no treatment control (Duman 2005), and in one study, published in abstract form only, the control arm intervention was not reported (Rafiq 2007). Of the 23 included studies, one paper reported an interim analysis (Selinger 2011) and one trial had two probiotic arms of differing dose (Gao 2010). To avoid unit of analysis errors we grouped the two probiotic arms together. To avoid losing important dose information for our subgroup meta-regression, we kept the probiotic arms intact and split the control group so that half served as comparator for each arm.

The overall pooled results using a complete case analysis favoured probiotics demonstrating a statistically significant reduction in the incidence of CDAD. The incidence of CDAD in the probiotic group was 2.0% compared to 5.5% in the placebo or no treatment control group (RR 0.36; 95% CI 0.26 to 0.51; random-effects) suggesting that 29 patients (95% CI 22 to 43) would need to be treated to prevent one case of CDAD (number needed to treat for an additional beneficial outcome). No statistically significant heterogeneity was detected for this comparison (P = 0.75; I squared = 0%). The forest plot for this outcome can be found in Figure 3.

Figure 3. Forest plot of comparison: 1 C. difficile associated diarrhea, outcome: 1.1 Incidence CDAD: complete case.



Seven of the 23 studies were rated as having a low risk of bias, while 16 were rated as having a high or unclear risk of bias. The low risk of bias studies suggested a stronger pooled protective effect of probiotics (RR 0.27; 95% CI 0.16 to 0.46) than the high risk of bias studies (RR 0.45; 95% CI 0.28 to 0.72) although a test of interaction between low and high or unclear risk of bias studies was not statistically significant (P = 0.16). Sixteen of 23 trials had missing CDAD data ranging from 5% to 45%. Using the assumed plausible ratios of event rates in those with missing data in comparison to those successfully followed: 1.5:1, 2:1, 3:1, and 5:1 (Akl 2012), our results were robust to all assumptions: even assuming a 5 to 1 ratio of events in those with missing data versus those with complete data in the intervention group - the effect was large and the confidence interval narrow (RR 0.57; 95% CI 0.38 to 0.85). Minimal heterogeneity was detected for this comparison (P = 0.08;I^2 = 33%).

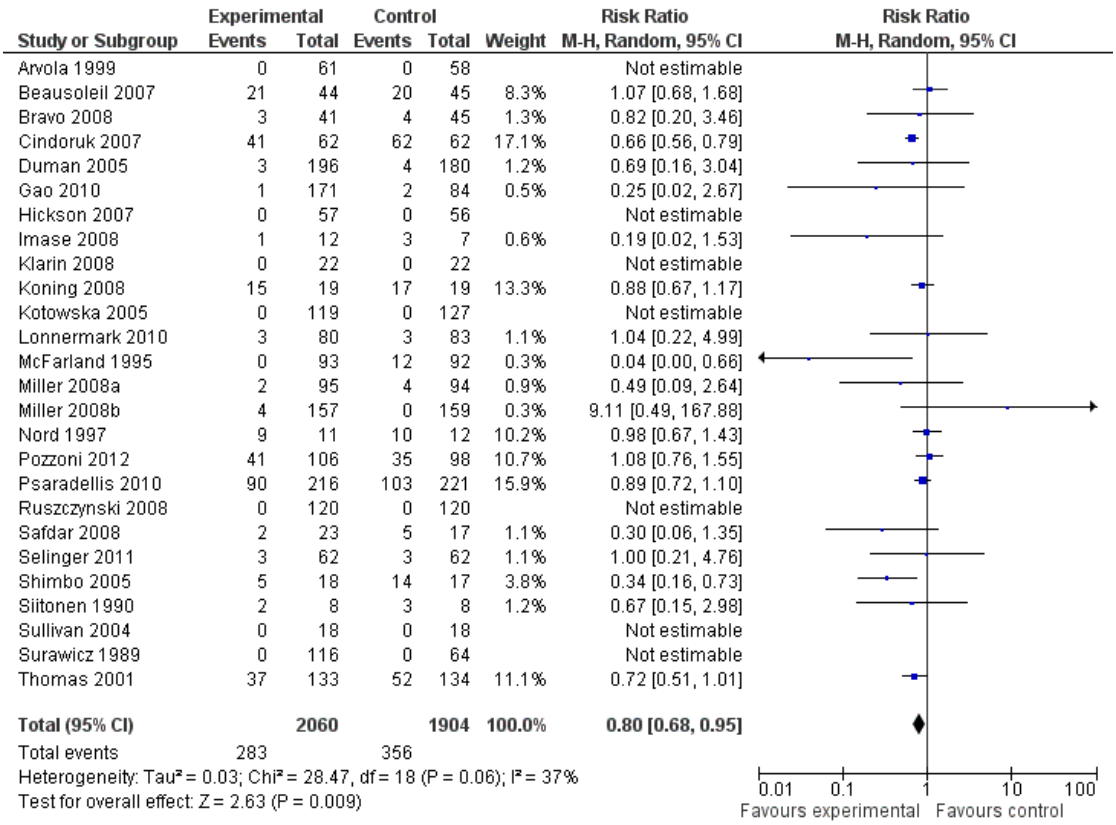
Incidence of *C. difficile* infection

Thirteen studies (n = 961) reported on the incidence of *C. difficile* infection. Of these, 11 were placebo-controlled and two trials used a no treatment control arm (Imase 2008; Shimbo 2005). One trial had two probiotic arms with different doses (Imase 2008) and we grouped the two probiotics arms together (with the exception of our investigation of dose effects where we adjusted as discussed above). The overall pooled results using a complete case approach did not show a statistically significant reduction in incidence of *C. difficile* infection. The incidence of *C. difficile* infection was 12.6% in the probiotics group compared to 12.7% in the placebo or no treatment control group (RR 0.89; 95% CI 0.64 to 1.24; random-effects). Three of the 13 studies were rated as having a low risk of bias and 10 were rated as having a high or unclear risk of bias. No statistically significant heterogeneity was detected for this comparison (P = 0.84; I squared = 0%).

Incidence of adverse events

Twenty-six of the included studies reported (n = 3964) on adverse events, seven of which reported no adverse events in either the treatment group or control group. Four of the included studies reported serious adverse events with none attributable to probiotic intervention (Miller 2008a; Miller 2008b; Pozzoni 2012; Psaradellis 2010). In both treatment and control groups the most common adverse events included abdominal cramping, nausea, fever, soft stools, flatulence, and taste disturbance. The incidence of reported adverse events in the probiotic group was 13.7% compared to 18.7% in the placebo or no treatment control group (RR 0.80; 95% CI 0.68 to 0.95), suggesting a statistically significant decrease in the number of reported adverse events in the probiotic group. Minimal heterogeneity was detected for this comparison; (P = 0.06; I^2 = 37%). Twelve of the 26 studies were rated as having a low risk of bias and 14 were rated as having a high or unclear risk of bias. The forest plot for this outcome can be found in Figure 4.

Figure 4. Forest plot of comparison: 2 Adverse events, outcome: 2.1 Adverse Events: complete case.



Fourteen of 26 trials had missing AE data ranging from 2% to 44%. Using the assumed plausible ratios of event rates in those with missing data in comparison to those successfully followed: 1.5:1, 2:1, 3:1, and 5:1 (Akl 2012), our results were not robust to all assumptions. Assuming a 2 to 1 ratio of events in those with missing data versus those with complete data in the intervention group - the effect was no longer statistically significant (RR 0.85; 95% CI 0.70 to 1.03). Moderate heterogeneity was detected for this comparison (P = 0.002; I^2 = 56%)..

Antibiotic-associated diarrhea

Twenty-five of the included studies (n = 4097) reported on antibiotic-associated diarrhea (AAD). Of these, 22 were placebo-controlled and three trials used a no treatment control arm (Duman 2005; Imase 2008; Shimbo 2005). One paper reported an interim analysis (Selinger 2011) and two trials had two probiotic arms of differing dose (Gao 2010; Imase 2008) which we grouped together as discussed above. The overall pooled results using a complete case analysis favoured probiotics demonstrating a statistically significant reduction in the incidence of AAD. Thirteen per cent of participants in the probiotics group developed AAD compared to 21% of the placebo or no treatment control group (RR 0.60; 95% CI 0.49 to 0.72). Statistically significant heterogeneity was detected for this comparison (P=0.04; I^2= 36%). Of these 25 studies, 13 were rated as having a low risk of bias and 12 were rated as having an unclear or high risk of bias.

Eleven of 25 trials had missing AAD data ranging from 4% to 43%. Using the assumed plausible ratios of event rates in those with missing data in comparison to those successfully followed: 1.5:1, 2:1, 3:1, and 5:1 (Akl 2012), our results were not robust to all assumptions. Assuming a 5 to 1 ratio of events in those with missing data versus those with complete data in the intervention group - the effect was no longer statistically significant (RR 0.90; 95% CI 0.69 to 1.18). A high degree of heterogeneity was detected for this comparison (P < 0.00001; I^2 = 78%).

Length of hospital stay

Three studies reported on length of hospital stay (Beausoleil 2007; Selinger 2011; Thomas 2001). Sufficient data for pooled analysis

were only available for one study (Beausoleil 2007). Contact was attempted with the authors of the remaining two trials, only one of which was successful (Selinger 2011). The combined mean difference for length of hospital stay using the two studies with sufficient data was -1.76 (95% CI -6.72 to 3.19) days and was not statistically significant. Using imputation (Higgins 2011) for a missing standard deviation value we calculated an effect size using all three trials which was also not statistically significant -0.32 (95% CI -3.21 to 2.57) days. Two trials were rated as having a low risk of bias for this outcome (Beausoleil 2007; Thomas 2001) and the other as unclear (Selinger 2011). No statistically significant heterogeneity was detected for this comparison (P = 0.29; I^2 = 20%).

Subgroup analysis

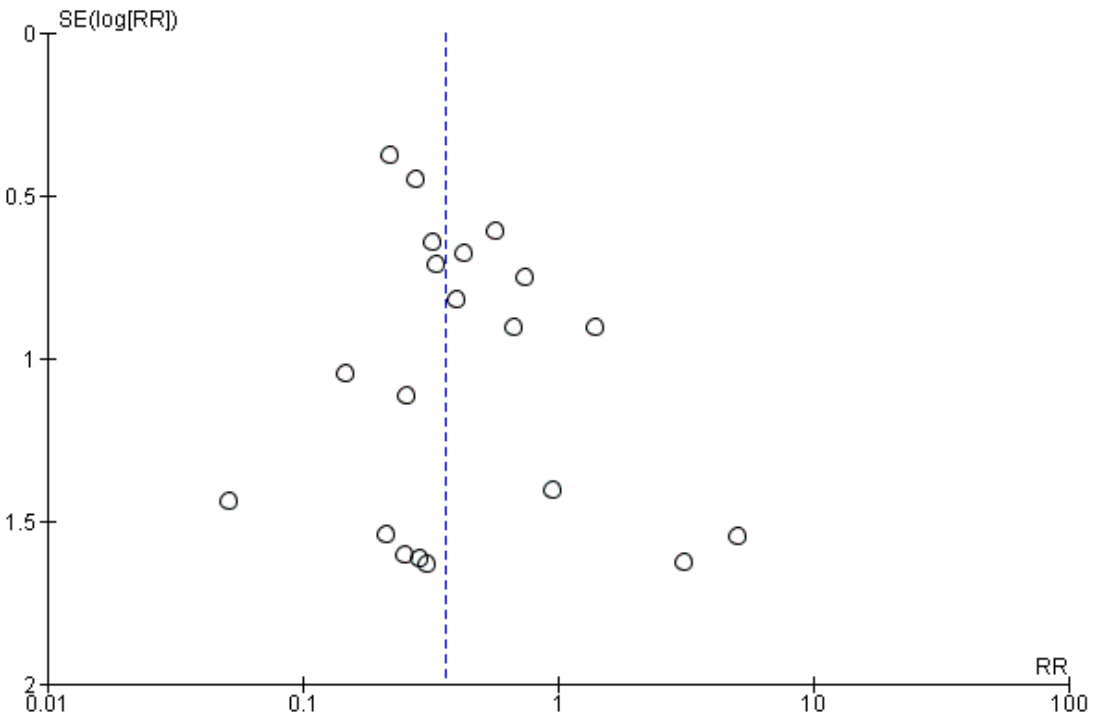
We considered the following *a priori* subgroups: dose, species, paediatric population, and risk of bias. With two exceptions, no subgroup comparisons resulted in a statistically significant test of interaction. The exceptions were noted when comparing the *L. acidophilus* + *L. casei* subgroup (RR 0.21; 95% CI 0.11 to 0.42, I^2 = 0%, n = 781) versus *Lactobacillus rhamnosus* subgroup (RR 0.63; 95% CI 0.30 to 1.33, I^2 = 88%, n = 1031) for the CDAD outcome and when comparing the adult subgroup (RR 0.63; 95% CI 0.51 to 0.76, I^2 = 35%, n = 3369) versus the child subgroup (RR 0.37; 95% CI 0.23 to 0.60, I^2 = 0%, n = 605) for the AAD outcome. Regarding the former, the test for interaction revealed statistically significant species related heterogeneity (P = 0.03). However, using 11 published criteria to evaluate the credibility of the subgroup analysis (Sun 2010), we consider the credibility of this subgroup effect as unlikely. That is, the subgroup effect is based on between study comparisons and is not consistent across studies, the direction of the subgroup effect was not pre-specified and we are unaware of any biological or direct evidence that suggests that *L. acidophilus* + *L. casei* is superior to *Lactobacillus rhamnosus*. A test for interaction between adult and child subgroups found heterogeneity (P=0.05) for the AAD outcome, suggesting that it is unlikely that chance can explain the heterogeneity. Using the criteria mentioned above we consider it possible that this is a credible subgroup effect. In particular, the subgroup is reasonably consistent across studies, there were a small number of a priori subgroups (four), and the subgroup and direction of effect were specified a priori.

Regarding patient population, one trial had exclusively outpatient data, 14 trials had inpatient data, five had mixed populations, and three were not specified. In *post hoc* analysis there was no statistical evidence of a subgroup difference (P = 0.64, I^2=0%).

Small study effects

Inspection of the funnel plots revealed no visual evidence of small study effects (e.g. publication bias) with the possible exception of AAD. The funnel plot for the primary outcome CDAD can be found in Figure 5. Additionally, using the Harbord linear regression test, we found no statistical evidence of small study effects (CDAD: P = 0.11; *C. difficile* infection: P = 0.56; Adverse events: P = 0.24; AAD: P = 0.31; Length of stay: n/a).

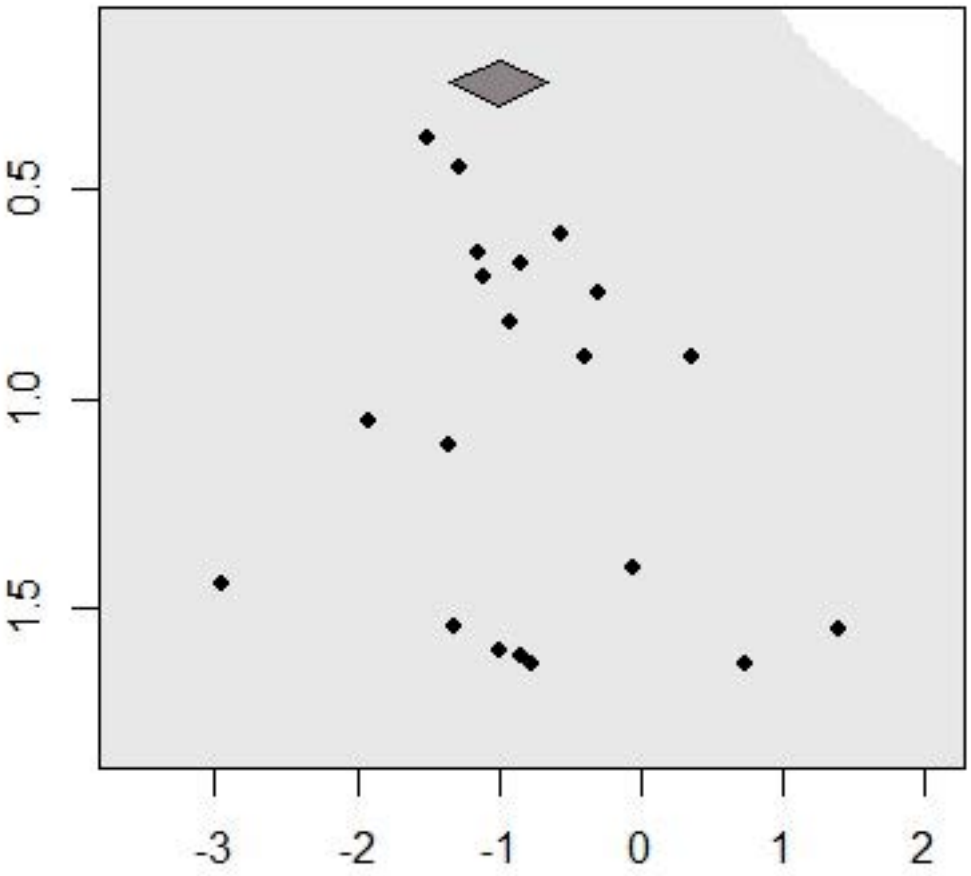
Figure 5. Funnel plot of comparison: 1 C. difficile associated diarrhea, outcome: 1.1 Incidence CDAD: complete case.



Contour enhanced funnel plots

Construction of contour enhanced funnel plots representing where a future trial would have to lie (in terms of standard error and effect size) for the cumulative effect estimate to no longer be statistically significant suggests that our results are robust even to theoretical large future trials with results in the opposite direction to those found in this review (e.g. that probiotics increases the risk of CDAD instead of decreasing it) (Figure 6).

Figure 6. Contour enhanced funnel plot for CDAD. The white area represents where a future trial would have to lay for the effect estimate to no longer be statistically significant.



Overall quality of evidence

We rated our results for the outcomes of CDAD, *Clostridium difficile* infection, and AE as having a 'moderate' level of evidence overall indicating that "further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate" (Guyatt 2008). We rated our results for the outcomes length of hospital stay and AAD as having a 'low' level of evidence indicating that "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" (Guyatt 2008). We downgraded the overall quality of evidence for CDAD to 'moderate' due to imprecision, as the calculated optimal information size (n = 8218) was more than the total sample size (n = 4213) (using an α of 0.05 and a β of 0.20 for a RRR of 30%). Additionally, overall events were few, totaling 154. We downgraded the overall quality of evidence for *C. difficile* infection to 'moderate' due to imprecision as well because the 95% confidence interval included both no effect and a substantial effect and the calculated optimal information size (n = 3024) was more than the total sample size (n = 961). In considering the overall evidence for the short-term use of probiotics in patients that are not immune-compromised or severely debilitated, we categorized the confidence in the effect estimates for adverse events as moderate. Only 26 of 31 trials reported on adverse events, an outcome that would presumably be documented in all probiotics trials, so we rated the quality of evidence down for selective reporting bias (Williamson 2005). We downgraded the overall quality of evidence for AAD to 'low' due to risk of bias associated with missing participant data and risk of publication bias (i.e., our search and eligibility criteria were specific to CDAD and as a result we likely missed trials that measured only AAD). We downgraded the level of evidence for length of

hospital stay to low due to risk of bias, as we suspect selective outcome reporting bias, and due to imprecision as the total sample size (n = 422) was less than the calculated optimal information size (n = 800). These overall quality of evidence assessments can be found in the Summary of findings for the main comparison

DISCUSSION

Summary of main results

The primary objective of this study was to investigate the use of probiotics to prevent CDAD in patients taking antibiotics. We identified 23 randomised controlled trials (4213 participants) investigating this clinical question. A complete case analysis of these trials suggests that probiotics reduce the risk of CDAD by 64% (RR 0.36; 95% CI 0.26 to 0.51; random-effects). These results proved robust to sensitivity analyses of worst plausible assumptions regarding missing outcome data and were similar whether considering trials in adults versus children, lower versus higher doses, different probiotic species, or higher versus lower risk of bias. Our judgment is that the overall evidence warrants moderate confidence in this large relative risk reduction (Summary of findings for the main comparison).

Interestingly, while we found evidence to suggest a large relative risk reduction in CDAD, the pooled results of the 13 trials (961 participants) investigating the incidence of *Clostridium difficile* infection did not indicate a statistically significant effect (RR 0.89; 95% CI 0.64 to 1.24). In our assessment, the evidence warrants moderate confidence in this result (Summary of findings for the main comparison). The possibility therefore arises that probiotics may be effective in preventing symptoms of infection or in limiting the extent of infection rather than inhibiting the colonization and infection itself. This question should be investigated further in future trials and may help elucidate the mechanisms by which probiotics prevent CDAD.

Twenty-six of the included studies (3964 participants) reported on adverse events. Compared to placebo or no treatment control, our pooled analysis indicates a statistically significant decrease in risk of adverse events among the probiotic group (RR 0.80; 95% CI 0.68 to 0.95). However, as is commonly the case with adverse event reporting, the authors' descriptions of adverse events were highly variable. We also believe there may be selective reporting bias. In consideration of these findings we conclude that for the short-term use of probiotics in patients that are not immunocompromised or severely debilitated, we consider the strength of the evidence supporting a decrease in the risk of adverse events to be moderate (Summary of findings for the main comparison).

Twenty-five of the included trials (4097 participants) reported on AAD. Our pooled analysis indicates a statistically significant decrease in the risk of AAD (RR 0.60; 95% CI 0.49 to 0.72). A sensitivity analysis using plausible and worst-plausible ratios of event rates in those with missing data in comparison to those successfully followed, demonstrated the AAD results were not robust to all assumptions (worst-plausible 5:1, RR 0.90; 95% CI 0.69 to 1.18). In addition we believe there was a potential for publication bias so we therefore rated the quality of the evidence as low. There was statistically significant heterogeneity across the 25 studies (P = 0.04; I^2 = 36%). Exploring this heterogeneity using *a priori* defined subgroups revealed that an adult versus pediatric subgroup effect may explain the observed heterogeneity (test of interaction: P = 0.05). Using 11 published criteria to evaluate subgroup effect credibility we consider it possible that the adult versus pediatric subgroup represents a credible subgroup effect . We therefore did not rate down further for inconsistency as the heterogeneity could be explained by age (Summary of findings for the main comparison).

Only three trials investigated the length of hospital stay. We did not find a statistically significant difference in length of hospital stay for those patients taking probiotics (MD -0.32, 95% CI -3.21 to 2.56).

Limitations

Other investigators have chosen not to pool trials using different species or strains of probiotics for the prevention of CDAD (Dendukuri 2005). In contrast, we chose to do so as we began with the hypothesis that the mechanism of action of various probiotics was similar and that any variation in effect would be due to chance. In investigating heterogeneity of effect size we did indeed find that the observed variability was consistent with that expected from chance (I^2 = 0). However, non-significant tests of statistical heterogeneity do not necessarily preclude significant clinical heterogeneity (Thompson 1994), so we considered the possibility of species differences in subgroup analysis (as we did with dose, population setting and age as well as risk of bias). We applied 11 published criteria to investigate subgroup effects (Sun 2010) and did not find convincing evidence to suggest their presence for CDAD. However, we did find a subgroup effect for AAD based on age (adults versus children). The subgroup hypothesis is sufficiently credible that it should be addressed in future studies.

There was significant missing data from multiple trials both in regards to patients lost to follow-up as well as the investigators' success in testing all fecal samples. To investigate the possible effect this might have had on our conclusions, we subjected this missing data to assumptions based on an extensive, but plausible sensitivity analysis (Akl 2012; Akl 2013). Our findings of reduced CDAD risk were robust to all sensitivity assumptions, while our findings of reduced risk of AAD were robust to all but the most extreme plausible sensitivity assumptions (assumed ratio of event rates 5:1),.

Strengths

We conducted an extensive literature search and identified 31 trials (4492 participants) for analysis including seven from our grey literature search (Cindoruk 2007; Rafiq 2007; Miller 2008a; Miller 2008b; Psaradellis 2010; Selinger 2011; Pozzoni 2012). For the most patient important CDAD outcome, we investigated statistical heterogeneity using the I^2 statistic (Higgins 2011) and found that the variation in effect sizes was compatible with that expected from chance (I^2 = 0%). We subsequently investigated the possibilities of subgroup effects including the risk of bias using 11 published criteria (Sun 2010). As suggested above, we also subjected missing participant data to a range of plausible assumptions, including worst plausible (assumed ratio of event rates 5:1) sensitivity analyses (Akl 2012). Because a correlation is sometimes observed between smaller trials and a more positive estimation of intervention effect, it is important to investigate possible 'small study effects' such as publication bias (Begg 1989, Sterne 2000). In line with recently developed small study effect guidelines (Sterne 2011) we opted to use the Harbord method which, while conceptually similar to the more familiar Egger method (Egger 1997), utilizes the efficient score and its variance and therefore avoids certain mathematical concerns inherent in the latter (Harbord 2006). Our investigation of publication bias revealed no graphical or statistical evidence of small study effects. To help visualize any fragility of results we also opted to include contour enhanced funnel plots in our analysis (Langan 2012). Finally, we independently applied GRADE criteria to determine the confidence in the estimate of effect (Guyatt 2008) for each of our outcomes.

Agreements and disagreements with other studies or reviews

We recently reported a systematic review and meta-analysis to determine the efficacy and safety of probiotics for the prevention of CDAD (Johnston 2012). Among the 20 included randomized trials, the pooled effect estimate reported as a relative risk was 0.34, which is very close to our pooled estimate. This Cochrane review identified an additional 3 trials reporting on CDAD and 9 trials reporting on adverse events, thus increasing the precision of our earlier results and further increasing the overall confidence in the estimate of effect. This review has also included additional outcomes of interest to decision makers, including the incidence of C. difficile infection and antibiotic associated diarrhea, and the length of hospital stay. Three recent systematic reviews have addressed the safety of probiotics (McFarland 2010; Whelan 2010; Hempel 2012). The most comprehensive of these reviews included all study designs involving humans and found no statistically significantly 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 spp*) (Hempel 2012).

AUTHORS' CONCLUSIONS

Implications for practice

Moderate quality evidence supports a large protective effect of probiotics in preventing CDAD (RR 0.36; 95% CI: 0.26, 0.51), but not in reducing the incidence of *Clostridium difficile* infection (RR 0.89; 95% CI: 0.64, 1.24). Stated in absolute terms, probiotic prophylaxis would prevent 35 CDAD episodes per 1000 patients treated. Low quality evidence supports a substantial protective effect of probiotics in preventing AAD (probiotics would prevent 84 AAD episodes per 1000 patients treated). Although adverse effects were reported among included trials, there were more adverse events among the patients in the control groups. Probiotics appear to be safe and effective when used as an adjunct to antibiotics in immunocompetent patients.

Implications for research

Although probiotics are clearly superior to placebo or no treatment for preventing CDAD, further head-to-head trials are warranted to distinguish optimal strains and dosages. These trials should be vigilant regarding minimizing losses to follow-up and other forms of missing participant data. Covariates of clinical interest such as strain, dose, baseline risk, age, length of treatment and antibiotic class, for example, need to be evaluated further. To allow for an accurate assessment of the potential for adverse events, especially among immunocompromised individuals, standardized and clear adverse event reporting is essential for future trials.

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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	Placebo controlled RCT, follow-up: 3 months post first antibiotic administration
Participants	Pediatric population, primarily outpatients (inpatients 5/119 outpatients 114/119), Finland, unclear if patients with recurrent *C. difficile* were included
Interventions	*L. rhamnosus GG 53103,* 40 x 10^9 cfu/day for duration of antibiotic treatment
Outcomes	CDAD, AAD and AE
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The patients were randomized by means of a computer program"
Allocation concealment (selection bias)	Unclear risk	No pertinent information provided, therefore it is unclear if allocation was successfully concealed. Empirical data from an analysis of 1346 trials suggests that unclear and inadequately concealed allocation can bias trials with unpredictable magnitude. However, unclear or inadequately concealed allocation was associated with bias only with subjective outcomes. There is little evidence of such bias with objective outcomes (Wood 2008)
Blinding of participants and personnel (performance bias) CDAD	Low risk	"*Lactobacillus GG* and placebo capsules were indistinguishable in appearance and taste" "All patients received the same information and the follow-up was conducted in a similar manner" "*Lactobacillus GG* and placebo capsules also were indistinguishable in appearance and taste when opened"
Blinding of participants and personnel (performance bias) AE	Low risk	See above: Blinding of participants and personnel (performance bias) CDAD

Arvola 1999 (*Continued*)

Blinding of participants and personnel (performance bias) AAD	Low risk	See above: Blinding of participants and personnel (performance bias) CDAD
Blinding of outcome assessment (detection bias) CDAD	Low risk	There was no explicit statement about blinding of 'outcome assessors.' The outcomes of interest in our review relevant to this study are CDAD, AE and AAD. The outcome of diarrhea was assessed by the parents of the participants. As the parents were blinded we consider this outcome to be assessed blind. In cases of diarrhea, samples were analyzed for *C. difficile*. There is no mention of blinding of the cytotoxin assay personnel although this is a placebo controlled drug trial so we will consider the risk of bias to be low here. Additionally, we consider the cytotoxin assay to be an 'objective outcome' which is less susceptible to bias based on inadequate blinding (Wood 2008)
Blinding of outcome assessment (detection bias) AE	Low risk	"The parents reported no adverse effects of *Lactobacillus GG* or placebo." While not explicitly mentioned as an outcome in the 'methods' section AE were reported on in 'results.' It appears AE were assessed via report from the parents who were blinded therefore we consider this outcome to be assessed blinded as well
Blinding of outcome assessment (detection bias) AAD	Low risk	The outcomes of interest in our review relevant to this study are CDAD, AE and AAD. The outcome of diarrhea was assessed by the parents of the participants. As the parents were blinded we consider this outcome to be assessed blind
Incomplete outcome data (attrition bias) CDAD	High risk	29% dropout. No mention of intention-to-treat analysis. Unbalanced loss to follow-up (20 placebo, 28 active) with only two observed events of *C. difficile*. It seems a per protocol analysis was done. As the event rates were extremely low we consider this a high risk of attrition bias
Incomplete outcome data (attrition bias) AE	High risk	See above: Incomplete outcome data (attrition bias) CDAD

Arvola 1999 (*Continued*)

Incomplete outcome data (attrition bias) AAD	High risk	See above: Incomplete outcome data (attrition bias) CDAD
Selective reporting (reporting bias)	Low risk	No independent protocol was identified. All outcomes declared in 'methods' were reported on in 'results.' While not listed explicitly as outcomes, viral and bacterial analyses including *C. difficile* assay were described in 'methods' and reported on in 'results.' In addition, while not described in 'methods' AE were reported on in 'results' as well
Other bias	Low risk	Funding sources listed and did not include industry sponsors. Baseline characteristics of participants included in analysis appeared roughly equal and evenly distributed. No other risk of bias identified

Beausoleil 2007

Methods	Placebo controlled RCT, follow-up: 3 weeks after last drug dose
Participants	Adult population, inpatient, Canada, 2/44 patients in the treatment arm and 4/45 in the control arm had a history of *C. difficile* infection
Interventions	Fermented milk containing *L. acidophilus* CL1285 and L. casei 25 x 10^9 cfu/day for 2 days then 50 x 10^9 cfu/day for duration of antibiotic course or placebo fermented milk
Outcomes	CDAD,AAD, and AE
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The method of randomization was not adequately reported in this paper
Allocation concealment (selection bias)	Unclear risk	No pertinent information provided, therefore it is unclear if allocation was successfully concealed
Blinding of participants and personnel (performance bias) CDAD	Low risk	"Both preparations were provided in identically labelled containers; their taste and texture were similar"

Blinding of participants and personnel (performance bias) AE	Low risk	See above: Blinding of participants and personnel (performance bias) CDAD
Blinding of participants and personnel (performance bias) AAD	Low risk	See above: Blinding of participants and personnel (performance bias) CDAD
Blinding of outcome assessment (detection bias) CDAD	Low risk	No explicit statement about blinding of 'outcome assessors.' The primary outcome of AAD was defined by stool frequency and consistency. It appears as if this assessment was done by the participant. Secondary outcomes include adverse events (also reported by the participant) and cytotoxin assay. The participants were blinded so those outcomes involving participant assessment are assumed to be assessed blinded. There is no mention of blinding of the cytotoxin assay personnel although this is a placebo controlled drug trial so we will consider the risk of bias to be low here. Additionally, we consider the cytotoxin assay to be an 'objective outcome' which is less susceptible to bias based on inadequate blinding (Wood 2008)
Blinding of outcome assessment (detection bias) AE	Low risk	See above: Blinding of outcome assessment (detection bias) CDAD
Blinding of outcome assessment (detection bias) AAD	Low risk	See above: Blinding of outcome assessment (detection bias) CDAD
Incomplete outcome data (attrition bias) CDAD	High risk	The testing of samples for *C. difficile* differed between groups:. 7 patients in active arm developed AAD, of these 2 were tested for *C. difficile,* 1 of whom was positive. In the placebo arm 16 patients developed AAD, yet 13 were tested for *C. difficile* and 7 were positive. It is unclear why all diarrhea samples were not tested as this was part of protocol stated in the 'methods.' Therefore for the outcomes involving *C. diffile* there is substantial incomplete outcome data that could have resulted in 'material' bias of results for these outcomes

Beausoleil 2007 (*Continued*)

Incomplete outcome data (attrition bias) AE	Low risk	There were no patients lost to follow-up
Incomplete outcome data (attrition bias) AAD	Low risk	There were no patients lost to follow-up
Selective reporting (reporting bias)	Low risk	A protocol for this study could not be identified. All outcomes discussed in 'methods' were reported in 'results'
Other bias	Low risk	"Product and placebo were provided by Bio-K+ International Inc, Laval, Quebec. A research grant was provided by Bio K+ International Inc to cover the pharmacy administration fees." While a producer of the active treatment was a financial sponsor no author is from the sponsoring agency

Bravo 2008

Methods	Placebo controlled RCT, follow-up: 9 days after last study drug dose
Participants	Mixed population (15 to 81 years of age), outpatient, Chile, unclear if patients with recurrent *C. difficile* were included
Interventions	*S. boulardi* 10.2 x 10^9 cfu/day for 12 days (duration of antibiotic course 5 to 10 days) or placebo
Outcomes	CDAD, AAD and AE
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The method of randomization was not described in this paper
Allocation concealment (selection bias)	Unclear risk	Not enough information provided
Blinding of participants and personnel (performance bias) CDAD	Low risk	"In a controlled randomized, double blind trial..."
Blinding of participants and personnel (performance bias) AE	Low risk	See above: Blinding of participants and personnel (performance bias) CDAD

Blinding of participants and personnel (performance bias) AAD	Low risk	See above: Blinding of participants and personnel (performance bias) CDAD
Blinding of outcome assessment (detection bias) CDAD	Low risk	There is no explicit mention of outcome assessor blinding. There is no mention of blinding of the cytotoxin assay personnel although this is a placebo controlled drug trial so we consider the risk of bias to be low here. Additionally, we consider the cytotoxin assay to be an 'objective outcome' which is less susceptible to bias based on inadequate blinding (Wood 2008)
Blinding of outcome assessment (detection bias) AE	Low risk	It appears AE were assessed by participants reporting to study personal all of whom were blinded
Blinding of outcome assessment (detection bias) AAD	Low risk	See above: Blinding of outcome assessment (detection bias) AE
Incomplete outcome data (attrition bias) CDAD	High risk	There were four losses to follow-up reported in this paper, two from each group. Analysis was done intention-to-treat although sensitivity analysis was performed for efficacy. All 86 participants who were enrolled and not excluded from onset due to exclusion criteria were analyzed. However, not all diarrhea samples were tested for *C. difficile*. Three participants in the active arm developed AAD. Of these patients, 3 were tested for *C. difficile*, 0 of which were positive for the toxin. In the placebo arm 5 participants developed AAD yet only 1 was tested for *C. difficile* and 0 were positive. Because 4 other placebo AAD cases were not evaluated for *C. difficile* we consider this a relatively high incomplete outcome rate for this outcome. For this reason we consider the CDAD outcome to have a high risk of 'material' bias
Incomplete outcome data (attrition bias) AE	Low risk	There were four losses to follow-up reported in this paper two from each group. Analysis was done intention-to-treat although sensitivity analysis was performed for efficacy. All 86 participants who were enrolled and not excluded from onset due

Bravo 2008 (*Continued*)

		to exclusion criteria were analyzed. We do not consider this small and balanced dropout rate to reasonably and 'materially' affect the AE reported event rate. For this reason we consider the outcome of AE to have a low risk of 'material' attrition bias
Incomplete outcome data (attrition bias) AAD	Low risk	See above: Incomplete outcome data (attrition bias) AE
Selective reporting (reporting bias)	Low risk	No protocol identified. All presumed outcomes from the 'methods' section were reported on in the 'results' section
Other bias	Low risk	"Funding: TUSCANY Laboratory." Funding was disclosed. It is unclear if TUSCANY produces the investigated product. No authors were associated with the funding organisation

Can 2006

Methods	Placebo controlled RCT, follow-up: 4 weeks after last antibiotic dose
Participants	Adult population, inpatient, Turkey, unclear if patients with recurrent *C. difficile* were included
Interventions	*S. boulardi* lyophilized 20 x 10^9 cfu/day $\leq$ 48 hours of antibiotic start dose (duration of study drug course not stated), additional information regarding length of probiotic treatment was unclear
Outcomes	CDAD and AAD
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The method of randomization was not adequately described
Allocation concealment (selection bias)	Unclear risk	No pertinent information provided and so it is unclear if allocation was successfully concealed
Blinding of participants and personnel (performance bias) CDAD	Low risk	"…a double-blind controlled study…"

Can 2006 (*Continued*)

Blinding of participants and personnel (performance bias) AAD	Low risk	See above: Blinding of participants and personnel (performance bias) CDAD
Blinding of outcome assessment (detection bias) CDAD	Low risk	No explicit statement about blinding of 'outcome assessors.' The outcome of diarrhea was assessed by the participants who were blinded. There is no mention of blinding of the cytotoxin assay personnel although this is a placebo controlled drug trial so in accordance with our *a priori* defined RoB criteria we will consider the risk of bias to be low here
Blinding of outcome assessment (detection bias) AAD	Low risk	The outcome of diarrhea was assessed by the participants who were blinded
Incomplete outcome data (attrition bias) CDAD	Low risk	No missing outcome data; number randomized is clearly stated and equal to number analysed. The risk of attrition bias is considered to be low for all outcomes
Incomplete outcome data (attrition bias) AAD	Low risk	See above: Incomplete outcome data (attrition bias) CDAD
Selective reporting (reporting bias)	Unclear risk	A protocol for this trial could not be identified. Outcomes were not explicitly mentioned as 'outcomes' in the 'methods' section although it seems they included AAD, *C. difficile*, microscopic and macroscopic stool examination, and type of antibiotic used. In the 'results' section all were reported with the exception of stool examination. This outcome is not particularly of interest in our review, however it is suggested that this domain be assessed at the study level not outcome level (Higgins 2011). It is also unclear how 'material' the bias to our review would be from this omission
Other bias	Low risk	"Source of support: Departmental sources. " No other source of bias identified

Cindoruk 2007

Methods	Placebo controlled RCT, follow-up: 6 weeks after last antibiotic dose
Participants	Adults, not specified, Turkey, unclear if patients with recurrent *C. difficile* were included
Interventions	*S. boulardi* 500 mg twice daily for 2 weeks
Outcomes	CDAD, AAD and AE
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was done using computer-based random numbers"
Allocation concealment (selection bias)	Unclear risk	Not specifically discussed.
Blinding of participants and personnel (performance bias) CDAD	Low risk	"Double blind"
Blinding of participants and personnel (performance bias) AE	Low risk	See above: Blinding of participants and personnel (performance bias) CDAD
Blinding of participants and personnel (performance bias) AAD	Low risk	See above: Blinding of participants and personnel (performance bias) CDAD
Blinding of outcome assessment (detection bias) CDAD	Low risk	CDAD assessment done by *C. difficile* toxin so risk of bias assumed to be low
Blinding of outcome assessment (detection bias) AE	Low risk	AE assessment filled out by participants who were blinded
Blinding of outcome assessment (detection bias) AAD	Low risk	No mention of how diarrhea was determined or assessed. Assumed to have been assessed by subjects who were blinded
Incomplete outcome data (attrition bias) CDAD	High risk	*C difficile* was only measured in a subset of diarrhea patients
Incomplete outcome data (attrition bias) AE	Unclear risk	No mention of patients lost to follow-up after treatment period. Diarrhea is listed with other AE

Cindoruk 2007 (*Continued*)

Incomplete outcome data (attrition bias) AAD	Unclear risk	Incomplete outcome data (attrition bias) AE
Selective reporting (reporting bias)	Low risk	No mention of a clinical trial register in text. Trial not found on clinicaltrials.gov. Outcome measures discussed in methods section were AE and *H pylori*. These outcomes were reported in results section. There was no explicit mention of a *C. difficile* outcome in the methods section although it was reported on in the results section
Other bias	Unclear risk	Baseline differences not statistically significant. No mention of funding sources

Duman 2005

Methods	No treatment controlled RCT, follow-up: 4 weeks after last study drug dose
Participants	17 to 81 yrs of age, not specified, Turkey, unclear if patients with recurrent *C. difficile* were included
Interventions	*S. boulardi* 30 x 10^9 cfu/day for 14 days (i.e. for duration of antibiotic course) or no treatment
Outcomes	CDAD, AAD and AE
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The method of randomization was not described
Allocation concealment (selection bias)	Unclear risk	No pertinent information provided so it is unclear if allocation was successfully concealed
Blinding of participants and personnel (performance bias) CDAD	Unclear risk	"This is a multicentre, prospective, open label and randomized study." This is an open label study and therefore there was knowledge of the allocated intervention and we consider this to have a high risk of performance bias. However, the magnitude of the bias may differ depending on the out-

		come in question. Additionally, there is little empirical evidence that objective outcomes are subject to bias due to lack of blinding (Wood 2008)
Blinding of participants and personnel (performance bias) AE	High risk	"This is a multicentre, prospective, open label and randomized study"
Blinding of participants and personnel (performance bias) AAD	Unclear risk	See above: Blinding of participants and personnel (performance bias) CDAD
Blinding of outcome assessment (detection bias) CDAD	Unclear risk	This is an open label study and therefore there was knowledge of the allocated intervention and we consider this to have a high risk of performance bias. Participants were not blinded and they self-reported diarrhea. Therefore these outcome assessments were definitely not blinded. There is no mention of blinding for microscopic and macroscopic investigation, nor for cytotoxin ELISA. However, we assume the assessors were not blinded as this was an open label trial. The magnitude of the bias may differ depending on the outcome in question. Additionally, there is little empirical evidence that objective outcomes are subject to bias due to lack of blinding (Wood 2008)
Blinding of outcome assessment (detection bias) AE	High risk	This is an open label study and therefore there was knowledge of the allocated intervention and we consider this to have a high risk of performance bias. Participants were not blinded and they self-reported adverse events. Therefore these outcome assessments were definitely not blinded
Blinding of outcome assessment (detection bias) AAD	Unclear risk	See above: Blinding of outcome assessment (detection bias) CDAD
Incomplete outcome data (attrition bias) CDAD	High risk	"The C. difficile toxin test was tested in the stool in 16 patients with diarrhea (11 in the control group and five in the treatment group) and it was positive only in one patient in the control group." Total diarrhea cases included 28 participants in con-

		trol group and 14 in treatment group. It appears that only one third of diarrhea cases in each group were assessed for *C. difficile*. We are very concerned with the risk of this missing outcome data especially considering the low event rate for the *C. difficile* and CDAD outcomes
Incomplete outcome data (attrition bias) AE	Low risk	It appears from the presentation of results that the analysis was done with intention-to-treat. All 389 patients randomized were analysed in their groups as randomized. Missing outcome data is balanced in numbers across intervention groups, with similar reasons for missing data across groups
Incomplete outcome data (attrition bias) AAD	Low risk	See above: Incomplete outcome data (attrition bias) AE
Selective reporting (reporting bias)	High risk	A protocol for this study was not identified. All outcomes discussed in 'methods' were reported in 'results.' However an additional outcome was reported in 'results' (cumulative diarrhea rate). Therefore the primary outcome of rate of diarrhea was "reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified." This classifies as a high risk of bias (Higgins 2011)
Other bias	Unclear risk	No mention of funding source. According to our *a priori* criteria for RoB assessment we will assess this as an unclear risk of bias

Gao 2010

Methods	Placebo controlled RCT with 2 actives arms (differing dose), follow-up: 3 weeks after last study drug dose
Participants	Adult population, inpatients, China, unclear if patients with recurrent *C. difficile* were included
Interventions	Probiotic arm 1: *L. acidophilus* CL1285 and *L. casei* LBC80R 50 x 10^9 cfu/day Probiotic arm 2: *L. acidophilus* CL1285 and *L. casei* LBC80R 100 x 10^9 cfu/day within 36 hours of antibiotic commencement until 5 days after discontinuation Placebo
Outcomes	CDAD, AAD and AE

Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"The randomization sequence used in this trial was generated by a computerized random-number generator (SAS, release 9.2; SAS Institute, Cary, NC) using a permuted block design that randomized among the three study groups while stratifying for age (50 - 59 vs. 60 - 70 years) and number of days on antibiotics (3 - 8 and 9 - 14 days)"
Allocation concealment (selection bias)	Low risk	"Study products were delivered to the investigative site in identical containers labelled only with the lot number and a sequentially numbered patient identification code"
Blinding of participants and personnel (performance bias) CDAD	Low risk	"This study was conducted using triple-blinding procedures. First, patients were blinded to the treatment received throughout the trial. Each patient received two pills each day, which were identical in shape, size, taste, smell, and color regardless of the assigned treatment group. Second, investigators and all involved clinicians were blinded to the treatment allocation throughout the course of the study. Finally, all study coordinators, clinical monitors, and biostatisticians were blinded to treatment allocation throughout the entire clinical study and until after all analyses were completed"
Blinding of participants and personnel (performance bias) AE	Low risk	See above: Blinding of participants and personnel (performance bias) CDAD
Blinding of participants and personnel (performance bias) AAD	Low risk	See above: Blinding of participants and personnel (performance bias) CDAD
Blinding of outcome assessment (detection bias) CDAD	Low risk	"This study was conducted using triple-blinding procedures. First, patients were blinded to the treatment received throughout the trial. Each patient received two

		pills each day, which were identical in shape, size, taste, smell, and color regardless of the assigned treatment group. Second, investigators and all involved clinicians were blinded to the treatment allocation throughout the course of the study. Finally, all study coordinators, clinical monitors, and biostatisticians were blinded to treatment allocation throughout the entire clinical study and until after all analyses were completed"
Blinding of outcome assessment (detection bias) AE	Low risk	See above: Blinding of outcome assessment (detection bias) CDAD
Blinding of outcome assessment (detection bias) AAD	Low risk	See above: Blinding of outcome assessment (detection bias) CDAD
Incomplete outcome data (attrition bias) CDAD	Low risk	No missing outcome data; number randomized is clearly stated and equal to number analysed. We consider the risk of attrition bias to be low for all outcomes
Incomplete outcome data (attrition bias) AE	Low risk	See above: Incomplete outcome data (attrition bias) CDAD
Incomplete outcome data (attrition bias) AAD	Low risk	See above: Incomplete outcome data (attrition bias) CDAD
Selective reporting (reporting bias)	Low risk	Protocol was listed with clinicaltrials.gov (NCT00958308). All primary and secondary outcomes listed in protocol were reported in the 'results'
Other bias	Unclear risk	"Bio-K + International (Laval, Quebec, Canada) provided financial support for this clinical trial. Sprim Advanced Life Sciences helped with study planning, conduct, and analysis and with paper development." Three paper authors work for Sprim which is a CRO which we assume was funded by Bio-K+ since they were the sponsor of the study. So while no sponsoring employees were authors the sponsoring agency contracted the organization that planned and analyzed the study

Hickson 2007

Methods	Placebo controlled RCT, follow-up: 4 weeks after last antibiotic or study drug dose
Participants	Adult population, inpatient, England, unclear if patients with recurrent *C. difficile* were included
Interventions	*L. casei imunitass* DN-114 001 19 x 10^9 cfu/day and *L. bulgaris* 1.9 x 10^9 cfu/day and *S. thermophilus* 19 x 10^9 cfu/day or placebo for length of course of antibiotics and for 1 week afterwards
Outcomes	CDAD, AAD and AE
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"An independent statistician generated the random allocation sequence, which was stratified for hospital, sex, and two age groups (50-69 and ≥70). The sequence was given to the pharmacy on each site." While no explicit mechanism of randomization was mentioned we will consider the involvement of an independent statistician to have led to an adequate randomization
Allocation concealment (selection bias)	Unclear risk	"The sequence was given to the pharmacy on each site." "The pharmacies removed the commercial labels, then applied study labels to identify the patient…" There is no explicit mention of allocation concealment. It appears the randomization sequence was delivered to the pharmacy and that the pharmacy assigned bottles directly to patients. While this suggests that the allocation was concealed we cannot be certain from this description and must consider as unclear
Blinding of participants and personnel (performance bias) CDAD	Low risk	"Actimel is sold in 100 g white plastic bottles with removable labels; Yazoo is packaged similarly but in 200 ml bottles. We chose Yazoo as placebo because it looks identical in colour and consistency to Actimel... The pharmacies removed the commercial labels, then applied study labels to identify the patient, the drink's "use by" date, and storage instructions. We could

		not find a placebo in an identical bottle to Actimel. Patients and researchers were blind to the study drink as they did not see the bottle the drink came in. Nursing staff dispensed the drinks and were instructed to pour 100 ml into a cup for the patient; they were not told which bottle contained which drink. Older people in the UK are not generally familiar with these products, but it is possible some patients might have recognized the taste. However, we had excluded people who regularly took this or other probiotic products from the study. Potential bias through unblinding was possible but unlikely." While there is potential for unblinding here the risk of 'material' bias is unclear and would depend on how many participants could identify based on taste and/or the interactions of nursing staff who may have recognized the bottles with the researchers and participants. Outcomes from this study which are pertinent to our review include AE (which we consider to be a subjective outcome) and CDAD (which we consider to be an objective outcome). Because the blinding is unclear we will assess the risk of 'material' performance bias in AE (subjective outcome) to be unclear while we consider the risk of 'material' performance bias in CDAD (objective outcome) to be low
Blinding of participants and personnel (performance bias) AE	Unclear risk	See above: Blinding of participants and personnel (performance bias) CDAD
Blinding of participants and personnel (performance bias) AAD	Low risk	See above: Blinding of participants and personnel (performance bias) CDAD
Blinding of outcome assessment (detection bias) CDAD	Low risk	"Microbiology staff who were blind to the study grouping assessed occurrence of *C. difficile* by analysis of a stool sample from patients who had diarrhea." We consider the CDAD outcome to have been assessed blind in this study and the risk of 'material' detection bias to be low

Blinding of outcome assessment (detection bias) AE	Unclear risk	It appears AE were assessed by the participants and reported to study staff. It is unclear if all participants were blind. For the purposes of this review we have classified AE as a subjective outcome and therefore we assess the risk of 'material' detection bias for AE to be unclear
Blinding of outcome assessment (detection bias) AAD	Low risk	See above: Blinding of outcome assessment (detection bias) CDAD
Incomplete outcome data (attrition bias) CDAD	Low risk	"We could not complete follow-up on 16% (22/135; 12 in probiotic group, 10 in placebo group) as we were unable to contact them at home despite numerous phone calls and written communications (16) or they had withdrawn (6) from the study, thus the analysis for occurrence of antibiotic associated diarrhea included 113 patients (56 in control and 57 in probiotic group). Four patients were not tested for C difficile (one in probiotic group, three in control group) and thus were not included in the analysis for occurrence of diarrhea associated with C difficile." The missing data were equally distributed between the two groups and the reasons for the missing data were similar in both groups. The missing data points are less likely to affect the authors' conclusions regarding the CDAD outcome in a 'material' way considering the event rates of 0 to 9
Incomplete outcome data (attrition bias) AE	High risk	Since there were no AE reported and the actual reasons given for dropout were not known for many participants it is possible that different AE rates due to intervention might have led to some dropout and since even a few events would change the results for this outcome (the comparison was 0 to 0) we therefore consider the risk of 'material' attrition bias to be high for this outcome
Incomplete outcome data (attrition bias) AAD	Low risk	Missing data were equally distributed between the two groups and the reasons for the missing data were similar in both groups

Selective reporting (reporting bias)	High risk	The trial was registered with the National Research Register under ID N0016106821. In the register the outcomes listed were: "Proportion of patients free of diarrhea in active & placebo groups, average length of stay compared in the two groups." The outcome of length of hospital stay which was listed in the register was not reported on as an outcome in the paper. Additionally the secondary outcome of CDAD which was listed in the paper was not listed in the register. Finally, the primary outcome of rate of diarrhea was "reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not prespecified" (Higgins 2011). This classifies as a high risk of bias according to Higgins. Considering all of these concerns we classify the risk of 'material' reporting bias to be high
Other bias	Unclear risk	"Funding: Healthcare Foundation and Hammersmith Hospital Trustees research committee and Danone Vitapole (Paris, France). The Healthcare Foundation made initial comments on the design of the study. Once funding was agreed none of the funding sources had any role in the data collection, analysis, interpretation of data, writing of the report, or the decision to submit the paper for publication "Competing interests: CJB, MH, and ALD'S have received funding from Danone to attend Danone International Conventions on Probiotics. CJB is a member of Danone UK advisory group The intervention is a product of Danone. While the study received funding from the producer of the product a clear statement was made regarding the conduct and design of the study. According to our *a priori* criteria for RoB assessment for funding we consider an industry/sponsor author to be a high risk of bias. In this case an author was a member of an industry/sponsor advisory group as opposed to an employee. The risk of bias in this regard is therefore unclear to us

Imase 2008

Methods	No treatment control three armed RCT (2 active arms of differing dose), follow-up: days 3 and 7 post treatment
Participants	Adult population, NS, Japan, unclear if patients with recurrent *C. difficile* were included
Interventions	Clostridium butyricum CBM588, one group 6 tablets / day x 7 days and one group 12 tablets/day x 7 days or no treatment
Outcomes	*C. difficile* incidence and AAD
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The method of randomization was not described
Allocation concealment (selection bias)	Unclear risk	No pertinent information provided so it is unclear if allocation was successfully concealed
Blinding of participants and personnel (performance bias) C. difficile incidence	Unclear risk	No pertinent information provided
Blinding of participants and personnel (performance bias) AAD	Unclear risk	No pertinent information provided
Blinding of outcome assessment (detection bias) C. difficile incidence	Unclear risk	No pertinent information provided
Blinding of outcome assessment (detection bias) AAD	Unclear risk	No pertinent information provided
Incomplete outcome data (attrition bias) C. difficile incidence	Low risk	No missing outcome data; number randomized is clearly stated and equal to number analysed. The risk of attrition bias is considered to be low for all outcomes
Incomplete outcome data (attrition bias) AAD	Low risk	See above: Incomplete outcome data (attrition bias) *C. difficile* incidence
Selective reporting (reporting bias)	Low risk	No protocol for this study was identified. The outcomes listed and described in 'methods' were those analysed in 'results'

Imase 2008 (*Continued*)

Other bias	High risk	No clear statement regarding financial conflict of interest or funding. "CBM588 (MIYA-BM tablets, Miyarisan Pharmaceutical, Tokyo, Japan) is a probiotic agent containing approximately 107 cfu per tablet." One of the authors is associated with the company that produces the probiotic tested. According to our *a priori* criteria for RoB assessment we will classify this as a high risk of bias

Klarin 2008

Methods	Placebo controlled RCT, follow-up: 2 times per week while patient was in ICU
Participants	Adult population, inpatients (ICU), Sweden, unclear if patients with recurrent *C. difficile* were included
Interventions	*Lactobacillus plantarum* 299v initially 9.6x 10^11 cfu/day and thereafter 8x10^10 cfu/day or placebo for length of ICU stay
Outcomes	*C. difficile* infection
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The method of randomization was not described
Allocation concealment (selection bias)	Unclear risk	"Randomisation was blinded to the investigators, the ward staff, and the sponsor (Probi AB, Lund, Sweden). Packages of the active and control study products came from an independent company." This description makes no explicit mention of allocation concealment. There is no indication that the intervention packages were sequentially numbered. Therefore, it is unclear if allocation was successfully concealed
Blinding of participants and personnel (performance bias) AE	Low risk	"Randomization was blinded to the investigators, the ward staff, and the sponsor. Packages of the active and control study

		products came from an independent company… The active study product consisted of a fermented oatmeal gruel containing 8 _ 108 colony-forming units (CFU)/ml of Lp299v (Probi AB). As a control, the same gruel without Lp299v bacteria but with lactic acid added to achieve the same pH was used… Enteral feeding was carried out"
Blinding of participants and personnel (performance bias) C. difficile incidence	Low risk	See above: Blinding of participants and personnel (performance bias) AE
Blinding of outcome assessment (detection bias) AE	Low risk	"Identification of C. difficile and testing for toxins were performed at the clinical microbiology departments at the hospitals. Lp299v was analysed in blinded samples… Furthermore, at the Lund University Hospital ICU, a second set of rectal swabs was collected on sampling days and sent blinded to Probi AB for analyses of lactobacilli, Enterobacteriaceae, sulphite-reducing clostridia, enterococci, and total viable count of anaerobes and Gram-negative bacteria"
Blinding of outcome assessment (detection bias) C. difficile incidence	Low risk	See above: Blinding of outcome assessment (detection bias) AE
Incomplete outcome data (attrition bias) AE	Low risk	"Forty-eight patients were included according to the protocol. Two patients declined participation, and two were excluded because the enteral feeding and the tested product were not given as instructed in the protocol. Thus, a total of 44 patients completed the study; 22 were given the active treatment and 22 received the control product" Only 8% missing outcome data
Incomplete outcome data (attrition bias) C. difficile incidence	Low risk	See above: Incomplete outcome data (attrition bias) AE
Selective reporting (reporting bias)	Low risk	A protocol for this study was not identified. Outcomes not explicitly stated as 'outcomes' in 'methods' although all those inferred to be outcomes were all reported in 'results'

Klarin 2008 (*Continued*)

Other bias	High risk	"Probi AB provided the study product and performed bacterial analyses as an unconditional grant. Two of the authors, B. J. and G. M., are shareholders in Probi AB." Probi AB produces the probiotic being tested. According to our *a priori* defined criteria for RoB assessment we assess this as a high risk of bias

Koning 2008

Methods	Placebo controlled RCT, follow-up: days 7, 14, 63
Participants	Adult population, outpatient, Netherlands, unclear if patients with recurrent *C. difficile* were included
Interventions	Multispecies (10) probiotic for total dose of 1x 10^10 cfu/day for 2 weeks or placebo
Outcomes	AAD, *C. difficile* infection and AE
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The method of randomization was not described
Allocation concealment (selection bias)	Unclear risk	"The treatment allocation was concealed to all investigators and volunteers, until the study had been completed and all analyses had been performed." While this trial claims that the allocation was concealed there is no description of the methods used for concealment
Blinding of participants and personnel (performance bias) AE	Low risk	"The study was executed according to a parallel, randomized, placebo-controlled, double-blind design"
Blinding of participants and personnel (performance bias) C. difficile incidence	Low risk	See above: Blinding of participants and personnel (performance bias) AE
Blinding of participants and personnel (performance bias) AAD	Low risk	See above: Blinding of participants and personnel (performance bias) AE

Blinding of outcome assessment (detection bias) AE	Low risk	The outcomes of AAD and AE were assessed by the participants who were blinded
Blinding of outcome assessment (detection bias) C. difficile incidence	Low risk	There is no explicit mention of blinding of the laboratory (e.g. cytotoxin assay) personnel although this is a placebo controlled drug trial so in accordance with our *a priori* defined RoB criteria we will consider the risk of bias to be low here
Blinding of outcome assessment (detection bias) AAD	Low risk	See above: Blinding of outcome assessment (detection bias) AE
Incomplete outcome data (attrition bias) AE	Low risk	"One subject in the probiotic group was found to be allergic to amoxycillin and had to be excluded.. Forty healthy volunteers completed the study"
Incomplete outcome data (attrition bias) C. difficile incidence	Low risk	There is no mention of noncompliance with fecal samples and it seems all groups were over 90% compliant with the placebo, intervention and antibiotic. From data representation in the paper it seems these two participants who did not complete the questionnaire were also excluded from analysis. In regards to *C. difficile* incidence, the two missing outcome data patients were from the placebo group so any unaccounted for *C. difficile* incidence in these participants would have actually favored the intervention effect estimate
Incomplete outcome data (attrition bias) AAD	Low risk	See above: Incomplete outcome data (attrition bias) AE
Selective reporting (reporting bias)	Low risk	A protocol for this study was not identified. Outcomes were not explicitly stated as such in 'methods' although all those inferred to be outcomes were all reported in 'results'
Other bias	Unclear risk	No explicit mention of conflict of interest. However, one of the authors is associated with the company that produces the study product. Our *a priori* defined criteria for assessment of funding bias considers a 'sponsor' as author to be a high risk of bias. While a study author is associated

		with the product being evaluated the funding appears to have come from a government agency. Additionally, no information regarding the roles of each author is provided so it is impossible to assess the role of the author connected to industry in planning the study or analysing the data. So while we identified a conflict of interest not reported in the paper we are unable to assess the role of this in creating 'material' bias in the effect estimates

Kotowska 2005

Methods	Placebo controlled RCT, follow-up: 2 weeks after last study drug dose
Participants	Pediatric population, mixed inpatient and outpatient, Poland, unclear if patients with recurrent *C. difficile* were included
Interventions	*S. boulardi* 10 x 10^9 cfu/day or placebo for duration of antibiotic course
Outcomes	CDAD, AAD and AE
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Investigators at the Medical University of Warsaw used computers to generate independent allocation sequences and randomization lists for each study site. To avoid a disproportionate number of patients in the experimental or placebo group, randomization at each site was performed in blocks of six (three received placebo and three, active treatment)"
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 of participants and personnel (performance bias) CDAD	Low risk	"All investigators, participants, outcome assessors and data analysts were blinded to the assigned treatment throughout the study" "The active treatment and placebo used

		in this study were prepared centrally by the hospital pharmacy at the Medical University of Warsaw as identically appearing wafers"
Blinding of participants and personnel (performance bias) AE	Low risk	See above: Blinding of participants and personnel (performance bias) CDAD
Blinding of participants and personnel (performance bias) AAD	Low risk	See above: Blinding of participants and personnel (performance bias) CDAD
Blinding of outcome assessment (detection bias) CDAD	Low risk	Outcome assessors were blinded
Blinding of outcome assessment (detection bias) AE	Low risk	Blinding of outcome assessment (detection bias) CDAD
Blinding of outcome assessment (detection bias) AAD	Low risk	Blinding of outcome assessment (detection bias) CDAD
Incomplete outcome data (attrition bias) CDAD	Low risk	"Overall, 23 (8.6%) of the randomized children [13 (9.8%) in the *S. boulardii* group and 10 (7.2%) in the placebo group] withdrew before completing the trial and were lost to follow-up. The reasons for not completing the trial were non-acceptance of the allocated intervention (n = 22) or damage of the study product (n = 1)." A relatively low number of participants had missing data post randomization. The missing data was balanced between groups both in number and reasons given for the missing outcome data. Additionally, an extreme case scenario regarding the missing data was calculated by the authors and shown to not influence the authors' conclusions. While it is unclear from the paper if this extreme case scenario was conducted for outcomes besides AAD (the authors' primary outcome), we consider the missing data to not realistically have a risk of 'material' bias on the authors' conclusions regarding CDAD

Kotowska 2005 (*Continued*)

Incomplete outcome data (attrition bias) AE	Low risk	There were no AE reported in either group. Although an extreme disproportion in AE event rates in the missing outcome data could have affected the estimate of AE it seems highly unlikely based on the rationale given for the missing data, null event rate in both groups, as well as the overall low amount of missing data
Incomplete outcome data (attrition bias) AAD	Low risk	See above; Incomplete outcome data (attrition bias) CDAD
Selective reporting (reporting bias)	Low risk	A protocol of this trial was not located. All outcomes listed in 'methods' were analysed in 'results.' We consider the risk of reporting bias to be low
Other bias	Unclear risk	Baseline participant characteristics roughly equivalent with no significant differences noted. No financial support, funding, or conflict of interest were listed. According to our *a priori* criteria for risk of funding bias we consider the risk of bias here to be unclear

Lewis 1998

Methods	Placebo controlled RCT, follow-up: every four days during length of treatment
Participants	Adult (elderly) population, inpatients, Wales, unclear if patients with recurrent *C. difficile* were included
Interventions	*S. boulardii* 226 mg/day or placebo for length of antibiotic treatment
Outcomes	*C. difficile* incidence and AAD
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The method of randomization was not described
Allocation concealment (selection bias)	Unclear risk	No pertinent information is provided so it is unclear if allocation was successfully concealed

Blinding of participants and personnel (performance bias) C. difficile incidence	Low risk	"The trial capsules were prepacked by the pharmacy such that the nursing staff dispensing them were blinded to which medication they were dispensing to the subjects. The medical management of each volunteer was by the attending physician and not influenced by the study"
Blinding of participants and personnel (performance bias) AAD	Low risk	See above: Blinding of participants and personnel (performance bias) *C. difficile* incidence
Blinding of outcome assessment (detection bias) C. difficile incidence	Low risk	Outcomes assessed by the nursing staff are assumed to be blinded as the nurses were blinded. There is no mention of blinding of the cytotoxin assay or cell culture personnel although this is a placebo controlled drug trial so in accordance with our *a priori* defined RoB criteria we will consider the risk of bias to be low here
Blinding of outcome assessment (detection bias) AAD	Low risk	See above: Blinding of outcome assessment (detection bias) *C. difficile* incidence
Incomplete outcome data (attrition bias) C. difficile incidence	Low risk	"Of 81 patients invited to participate in the study, 72 agreed and were randomized. Three subjects failed to complete the study because they did not wish to have stool specimens collected." From the presentation of their results it seems 69 participants were included in analysis therefore it seems the missing outcomes data are for the 3 who did not complete the study. It is not clear from which group those three belonged. However, the reason given for the missing outcome data (not wishing to collect stool specimens) is unlikely to be related to the true outcome. Additionally, even assuming high event rates for each outcome from the missing data there would be little effect on the conclusion reached by the study authors. Therefore, we will consider the risk of attrition bias here to be low for all outcomes
Incomplete outcome data (attrition bias) AAD	Low risk	See above: Incomplete outcome data (attrition bias) *C. difficile* incidence

Lewis 1998 (*Continued*)

Selective reporting (reporting bias)	Low risk	A protocol for this study was not identified. Outcomes not explicitly stated as such in 'methods' although all those inferred to be outcomes were all reported in 'results'
Other bias	Low risk	This paper appears to be free of baseline imbalances and funding conflicts. No other sources of bias identified

Lonnermark 2010

Methods	Placebo controlled RCT, follow-up: depending on outcome last day of study drug or 3 weeks post treatment
Participants	Adult population, mixed inpatient and outpatient, Sweden, unclear if patients with recurrent *C. difficile* were included
Interventions	*L. plantarum* 299v 10 x 10^9 cfu/day or placebo within 48 hours of antibiotic commencement until 7 days after discontinuation
Outcomes	CDAD, AAD, AE, and *C. difficile* incidence
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Computer-generated randomization lists were used to allocate patients to either treatment group"
Allocation concealment (selection bias)	Low risk	"Staff at Ska' nemejerier, who at no time had direct contact with the patients or investigators, labelled the test drink packages according to the randomization schedule"
Blinding of participants and personnel (performance bias) CDAD	Low risk	"The study was double blind and placebo controlled"
Blinding of participants and personnel (performance bias) AE	Low risk	See above: Blinding of participants and personnel (performance bias) CDAD
Blinding of participants and personnel (performance bias) C. difficile incidence	Low risk	See above: Blinding of participants and personnel (performance bias) CDAD

Blinding of participants and personnel (performance bias) AAD	Low risk	See above: Blinding of participants and personnel (performance bias) CDAD
Blinding of outcome assessment (detection bias) CDAD	Low risk	The outcomes of diarrhea as well as other secondary outcomes such as A.E. were assessed by the participants who were blinded. There is no mention of blinding of the cytotoxin assay personnel although this is a placebo controlled drug trial so in accordance with our *a priori* defined RoB criteria we will consider the risk of bias to be low here
Blinding of outcome assessment (detection bias) AE	Low risk	See above: Blinding of outcome assessment (detection bias) CDAD
Blinding of outcome assessment (detection bias) C. difficile incidence	Low risk	See above: Blinding of outcome assessment (detection bias) CDAD
Blinding of outcome assessment (detection bias) AAD	Low risk	See above Blinding of outcome assessment (detection bias) CDAD
Incomplete outcome data (attrition bias) CDAD	Unclear risk	"Among the 76 patients who left the study, 38 were randomized to L. plantarum 299v and 38 to placebo. The reasons for not completing the study did not differ between these groups of individuals (data not shown). A comparison between the patients who remained in the study and patients who did not is presented in Table 1. The drop-outs were significantly younger than the patients completing the study (P= 0.0015)." Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups (when reasons were known). However, the number of drop outs is very large and we have no reason given for drop out for 31 participants. In addition, event rates were very low for both objective and subjective outcomes. Due to these concerns we will assess as unclear risk of attrition bias for all outcomes

Lonnermark 2010 (*Continued*)

Incomplete outcome data (attrition bias) AE	Unclear risk	See above: Incomplete outcome data (attrition bias) CDAD
Incomplete outcome data (attrition bias) C. difficile incidence	Unclear risk	See above: Incomplete outcome data (attrition bias) CDAD
Incomplete outcome data (attrition bias) AAD	Unclear risk	See above: Incomplete outcome data (attrition bias) CDAD
Selective reporting (reporting bias)	Low risk	Outcomes clearly stated in 'methods' all of which were analysed in 'results.'
Other bias	High risk	The study product being investigated in this study is sold by Probi AB. Financial support came from Probi AB. One of the authors is associated with Probi AB. Three authors hold stock in Probi AB. According to our *a priori* defined RoB criteria for funding bias we assess this as a high risk of bias

McFarland 1995

Methods	Placebo controlled RCT, follwo-up: 7 weeks after last study drug dose
Participants	Adult population, inpatient, USA, unclear if patients with recurrent *C. difficile* were included
Interventions	*S. boulardi* lyophilized 30 x 10^9 cfu/day or placebo within 72 hours of antibiotic commencement until 3 days after discontinuation
Outcomes	CDAD, AAD, AE, and *C. difficile* incidence
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The method of randomization was not described
Allocation concealment (selection bias)	Unclear risk	No pertinent information provided
Blinding of participants and personnel (performance bias) CDAD	Low risk	"A double-blinded…trial." "The appearance and odor of the capsules of the patented *S. boulardii* and placebo

		were identical. The 1:1 (*S. boulardii*: placebo) randomization and packaging of the blinded study kits was performed at Laboratoires Biocodex (Montrouge, France) to ensure that the study investigators did not have access to the identity of the study drug"
Blinding of participants and personnel (performance bias) AE	Low risk	See above: Blinding of participants and personnel (performance bias) CDAD
Blinding of participants and personnel (performance bias) C. difficile incidence	Low risk	See above: Blinding of participants and personnel (performance bias) CDAD
Blinding of participants and personnel (performance bias) AAD	Low risk	See above: Blinding of participants and personnel (performance bias) CDAD
Blinding of outcome assessment (detection bias) CDAD	Low risk	"The etiology of all cases of diarrhea was determined independently by three blinded investigators." The outcomes from this trial pertinent to our review include CDAD, C. diff incidence, and AE. It appears diarrhea and AE were reported by patients to study investigators, all of whom were blinded. In addition, the assessment of CDAD was explicitly described as assessed blinded. While not explicitly mentioned in the text of the paper, it would appear likely that the *C. difficile* incidence was assessed in a similar blinded manner.For these reasons we consider the risk of 'material' detection bias for the outcomes CDAD, C. diff incidence, and AE to be low
Blinding of outcome assessment (detection bias) AE	Low risk	See above: Blinding of outcome assessment (detection bias) CDAD
Blinding of outcome assessment (detection bias) C. difficile incidence	Low risk	See above: Blinding of outcome assessment (detection bias) CDAD
Blinding of outcome assessment (detection bias) AAD	Low risk	See above: Blinding of outcome assessment (detection bias) CDAD

Incomplete outcome data (attrition bias) CDAD	High risk	There are missing data from 33% of randomized participants. The authors claim that there was no significant difference in study group assignment between those censored and those remaining in the trial. In addition, while censored participants did have significantly different outcomes than the rest of randomized patients (e.g. AAD) the authors claim there was no significant difference based upon the type of study drug assigned. However, the raw numbers of missing outcome data per study group are not provided. Considering the extremely high missing outcome data rate we must consider the risk of 'material' attrition bias for the low event rate outcomes of CDAD and C. diff incidence to be high
Incomplete outcome data (attrition bias) AE	Low risk	96% of adverse event forms for all randomized patients were available for analysis. Therefore, we consider the risk of 'material' attrition bias to be low for the AE outcome
Incomplete outcome data (attrition bias) C. difficile incidence	High risk	See above: Incomplete outcome data (attrition bias) CDAD
Incomplete outcome data (attrition bias) AAD	High risk	See above: Incomplete outcome data (attrition bias) CDAD
Selective reporting (reporting bias)	Low risk	No protocol identified. 'Outcomes' were not explicitly listed although all outcomes and statistical analyses inferred from the 'methods' section were analysed in the 'results' section
Other bias	High risk	This study was free of baseline imbalances. "The study was funded by grants to University of Kentucky, University of Washington, and St. Louis University Medical Center from Laboratoires Biocodex, Montrouge, France." The primary author is associated with a company that both produces S. boulardii and funded the trial. According to our *a priori* determined criteria for risk of funding bias we consider this to constitute a high risk of 'material' bias

Miller 2008a

Methods	Placebo controlled RCT, follow-up: not stated
Participants	Adult population, inpatient, Canada, unclear if patients with recurrent *C. difficile* were included
Interventions	*LGG* capsules (4 x 10^{10} cfu /day) or placebo for 14 days
Outcomes	CDAD and AE
Notes	unpublished

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Follow up with authors revealed that they used computers for generation of randomization
Allocation concealment (selection bias)	Unclear risk	No pertinent information provided, therefore it is unclear if allocation was successfully concealed
Blinding of participants and personnel (performance bias) CDAD	Low risk	"We conducted two randomized, double-blind studies"
Blinding of participants and personnel (performance bias) AE	Low risk	See above: Blinding of participants and personnel (performance bias) CDAD
Blinding of outcome assessment (detection bias) CDAD	Low risk	"Diarrhea stool was tested for *C. difficile* toxin." There is no mention of blinding of the cytotoxin assay personnel although this is a placebo controlled drug trial so we will consider the risk of bias to be low here
Blinding of outcome assessment (detection bias) AE	Low risk	While the only AE reported was mortality it was assessed as not related to intervention. Nevertheless mortality is an obviously objective outcome and so for both AE and CDAD we assess the risk of 'material' bias to be low
Incomplete outcome data (attrition bias) CDAD	Low risk	No loss to follow up

Miller 2008a (*Continued*)

Incomplete outcome data (attrition bias) AE	Low risk	See above: Incomplete outcome data (attrition bias) CDAD
Selective reporting (reporting bias)	Unclear risk	No protocol identified. This was an unpublished abstract so unclear if methods section would match with results section. We consider the risk of 'material' reporting be unclear
Other bias	High risk	Conagra supported the study and produces the product. It is unclear what role or access Conagra had with design, conduct, and analysis of the studies. "Dr. Miller has received research grants, acts as a consultant, or serves on an advisory board for the following: Biomerieux, ConAgra, Convatec, Genzyme, Iroko, Merck, Novartis, Optimer, Salix, Wyeth." Primary author has financial relationship with the company funding the trials and producing the trial intervention. According to our *a priori* defined criteria for RoB assessment we assess this as a high risk of bias

Miller 2008b

Methods	Placebo controlled RCT, follow-up: not stated
Participants	Adult population, inpatient, Canada, unclear if patients with recurrent *C. difficile* were included
Interventions	LGG 12 x 10^{10} cfu /day or placebo for 14 days
Outcomes	CDAD, AAD and AE
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Follow up with authors revealed that they used computers for generation of randomization

Allocation concealment (selection bias)	Unclear risk	No pertinent information provided, therefore it is unclear if allocation was successfully concealed
Blinding of participants and personnel (performance bias) CDAD	Low risk	"We conducted two randomized, double-blind studies"
Blinding of participants and personnel (performance bias) AE	Low risk	See above: Blinding of participants and personnel (performance bias) CDAD
Blinding of participants and personnel (performance bias) AAD	Low risk	See above: Blinding of participants and personnel (performance bias) CDAD
Blinding of outcome assessment (detection bias) CDAD	Low risk	"Diarrhea stool was tested for C. difficile toxin." There is no mention of blinding of the cytotoxin assay personnel although this is a placebo controlled drug trial so we will consider the risk of bias to be low here
Blinding of outcome assessment (detection bias) AE	Low risk	While the only AE reported was mortality it was assessed as not related to intervention. Nevertheless mortality is an obviously objective outcome and so for both AE and CDAD we assess the risk of 'material' bias to be low
Blinding of outcome assessment (detection bias) AAD	Low risk	Diarrhea assessment was from blinded personnel
Incomplete outcome data (attrition bias) CDAD	Unclear risk	There is some confusion in abstract and materials provided by authors. In Miller 2008b the abstract says there was 1 LTFU in the LGG group and 4 in placebo group. But it also says by the end there were 3 LTFU. It is unclear if these are additional LTFU and what group the 3 were in. Communication with authors could not resolve this
Incomplete outcome data (attrition bias) AE	Unclear risk	See above: Incomplete outcome data (attrition bias) CDAD
Incomplete outcome data (attrition bias) AAD	Unclear risk	See above: Incomplete outcome data (attrition bias) CDAD

Miller 2008b (*Continued*)

Selective reporting (reporting bias)	Unclear risk	No protocol identified. This was an unpublished abstract so unclear if methods section would match with results section. We consider the risk of 'material' reporting be unclear
Other bias	High risk	Conagra supported the study and produces the product. It is unclear what role or access conagra had with design, conduct, and analysis of the studies. "Dr. Miller has received research grants, acts as a consultant, or serves on an advisory board for the following: Biomerieux, ConAgra, Convatec, Genzyme, Iroko, Merck, Novartis, Optimer, Salix, Wyeth." Primary author has financial relationship with the company funding the trials and producing the trial intervention. According to our *a priori* defined criteria for RoB assessment we assess this as a high risk of bias

Nord 1997

Methods	Placebo controlled RCT, follow-up: 21 days post antibiotic treatment
Participants	Adult population, healthy, Sweden, unclear if patients with recurrent *C. difficile* were included
Interventions	*Bifidobacterium bifidum* and *Lactobacillus acidophilus* 2x10^10 cfu/day or placebo for 14 days
Outcomes	*C. difficile* incidence and AE
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The method of randomization was not described
Allocation concealment (selection bias)	Unclear risk	No pertinent information provided, therefore it is unclear if allocation was successfully concealed

Nord 1997 (*Continued*)

Blinding of participants and personnel (performance bias) AE	Low risk	"The investigation was performed as a randomized double-blind parallel group study…"
Blinding of participants and personnel (performance bias) C. difficile incidence	Low risk	See above: Blinding of participants and personnel (performance bias) AE
Blinding of outcome assessment (detection bias) AE	Low risk	The outcomes pertinent to our review from this trial include AE and *C. difficile* incidence. It appears AE were observed by study personnel and/or reported to them by the participants all of which were blinded. There is no explicit mention of blinding of laboratory personnel who would have assessed the *C. difficile* incidence outcome. However, this is a placebo controlled drug trial so in accordance with our *a priori* defined RoB criteria we will consider the risk of bias to be low here
Blinding of outcome assessment (detection bias) C. difficile incidence	Low risk	Blinding of outcome assessment (detection bias) AE
Incomplete outcome data (attrition bias) AE	Low risk	It appears all outcome data were available from all randomized participants
Incomplete outcome data (attrition bias) C. difficile incidence	Low risk	See above: Incomplete outcome data (attrition bias) AE
Selective reporting (reporting bias)	Low risk	No protocol identified and no explicit listing of "outcomes" in the 'methods' section. However, all assumed outcomes discussed in 'methods' were analysed in 'results'
Other bias	Unclear risk	No other source of bias identified. No mention of funding source. According to our *a priori* criteria for RoB assessment we will assess this as an unclear risk of bias

Plummer 2004

Methods	Placebo controlled RCT, follow-up: last day of study drug
Participants	Adult population (elderly), inpatient, England, unclear if patients with recurrent *C. difficile* were included

Plummer 2004 (*Continued*)

Interventions	*L. acidophilus* and *B. bifidum* 20 x 10^9 cfu/day or placebo within 36 hours of antibiotic commencement then for 20 days	
Outcomes	CDAD, AAD and *C. difficile* incidence	
Notes		

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The method of randomization was not described
Allocation concealment (selection bias)	Unclear risk	No pertinent information provided and so it is unclear if allocation was successfully concealed
Blinding of participants and personnel (performance bias) CDAD	Low risk	"The trial was a double blind, placebo-controlled study…"
Blinding of participants and personnel (performance bias) C. difficile incidence	Low risk	See above: Blinding of participants and personnel (performance bias) CDAD
Blinding of participants and personnel (performance bias) AAD	Low risk	See above: Blinding of participants and personnel (performance bias) CDAD
Blinding of outcome assessment (detection bias) CDAD	Low risk	The outcomes of this study pertinent to our review include CDAD and *C. difficile* incidence. Both of these outcomes were assessed via culture and immunologic laboratory measures. There is no mention of blinding of the laboratory personnel although this is a placebo controlled drug trial so in accordance with our *a priori* defined RoB criteria we will consider the risk of bias to be low here
Blinding of outcome assessment (detection bias) C. difficile incidence	Low risk	See above: Blinding of outcome assessment (detection bias) CDAD
Blinding of outcome assessment (detection bias) AAD	Low risk	See above: Blinding of outcome assessment (detection bias) CDAD

Plummer 2004 (*Continued*)

Incomplete outcome data (attrition bias) CDAD	Low risk	"Of the randomised patients, 138 completed the study, 69 with probiotics in conjunction with antibiotics and 69 with antibiotics alone." "150 patients were recruited and 138 patients fulfilled the inclusion criteria. For these patients, bowel habit on admission and prescribed medication were recorded." It appears that for all eligible participants that were randomized all outcome data was available. We consider the risk of 'material' attrition bias to be low for all outcomes
Incomplete outcome data (attrition bias) C. difficile incidence	Low risk	See above: Incomplete outcome data (attrition bias) CDAD
Incomplete outcome data (attrition bias) AAD	Low risk	See above: Incomplete outcome data (attrition bias) CDAD
Selective reporting (reporting bias)	Low risk	No protocol identified. No explicit disclosure of 'outcomes' to be addressed although all inferred outcomes from 'methods' section were analyzed in 'results'
Other bias	High risk	There is no direct mention of study funding although it is disclosed that the study product was provided by Cultech. The primary author is an employee of the company (Cultech) that produces the study product. Although funding is not explicitly disclosed, we consider it likely that the trial was funded by Cultech. Due to these considerations we consider the risk of 'material' bias here to be high

Pozzoni 2012

Methods	Placebo controlled RCT, follow-up: 12 weeks after last antibiotic dose
Participants	Adult population (> 50 years of age), inpatient, Italy, unclear if patients with recurrent C. difficile were included
Interventions	*Saccharomyces Boulardii* $10x10^9$ cfu/day or placebo within 48 hours of antibiotic commencement for length of antibiotic treatment and then for 7 days afterwards
Outcomes	CDAD, AAD, and AE

Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"...computer-generated random-number table"
Allocation concealment (selection bias)	Low risk	"Central randomisation by hospital pharmacy.."
Blinding of participants and personnel (performance bias) CDAD	Low risk	"The *S. boulardii* and placebo tablets were identical in shape, size, taste, smell, and color. The participants, researchers, and staff contributing to the study (doctors, nurses, and microbiologists) were unaware of the treatment allocations throughout the duration of the study"
Blinding of participants and personnel (performance bias) AE	Low risk	See above: Blinding of participants and personnel (performance bias) CDAD
Blinding of participants and personnel (performance bias) AAD	Low risk	See above: Blinding of participants and personnel (performance bias) CDAD
Blinding of outcome assessment (detection bias) CDAD	Low risk	"The participants, researchers, and staff contributing to the study (doctors, nurses, and microbiologists) were unaware of the treatment allocations throughout the duration of the study"
Blinding of outcome assessment (detection bias) AE	Low risk	See above: Blinding of outcome assessment (detection bias) CDAD
Blinding of outcome assessment (detection bias) AAD	Low risk	See above: Blinding of outcome assessment (detection bias) CDAD
Incomplete outcome data (attrition bias) CDAD	High risk	25% of patients in the treatment group were lost to follow-up and 27% of placebo patients were lost to follow-up It appears that patients were only evaluated for C. difficile if the diarrhea occurred in the hospital It seems only 29 patients developed diar-

		rhea. Of these 22, developed diarrhea out of hospital and only 2 patients were tested for *C. difficile*. Therefore 20/29 cases of diarrhea were not tested for *C. difficile*
Incomplete outcome data (attrition bias) AE	Low risk	All patients who discontinued where investigated for rationale and none reported withdrawal due to AE
Incomplete outcome data (attrition bias) AAD	Unclear risk	High LTFU, unclear what effect this has on AAD outcome
Selective reporting (reporting bias)	Low risk	The study is registered under ISRCTN number ISRCTN86623192 (http://www.controlled-trials.com/ISRCTN86623192/). The reported outcomes are identical to those published in protocol
Other bias	Low risk	This study was supported financially by an *ad hoc* hospital fund for independent research. No funding biases noted. No significant baseline differences between groups

Psaradellis 2010

Methods	Placebo controlled RCT, follow-up: 3 weeks after last study drug dose
Participants	Adult population, mixed inpatient and outpatient, Canada, unclear if patients with recurrent *C. difficile* were included
Interventions	Placebo or *L. acidophilus* CL1285 and *L. casei* 25 x 10^9 cfu/day for 2 days then 50 x 10^9 cfu/day until 5 days after discontinuation of antibiotic
Outcomes	CDAD, AAD, and AE
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The method of randomization was not described
Allocation concealment (selection bias)	Unclear risk	Not enough information provided

Blinding of participants and personnel (performance bias) CDAD	Low risk	"This was a multicenter double-blind, randomized, placebo controlled, study…"
Blinding of participants and personnel (performance bias) AE	Low risk	See above: Blinding of participants and personnel (performance bias) CDAD
Blinding of participants and personnel (performance bias) AAD	Low risk	See above: Blinding of participants and personnel (performance bias) CDAD
Blinding of outcome assessment (detection bias) CDAD	Low risk	There is no explicit mention of outcome assessor blinding. Outcomes of interest to our review from this trial include AE and CDAD. There is no mention of blinding of the cytotoxin assay personnel although this is a placebo controlled drug trial so we will consider the risk of bias to be low here
Blinding of outcome assessment (detection bias) AE	Low risk	"Safety was assessed by the incidence of treatment emergent adverse events, which were reported according to the MedDRA (version 10.1) dictionary of terms." It appears AE were assessed by participants reporting to study personal all of whom were blinded and that an objective dictionary of terms was used for reported adverse events
Blinding of outcome assessment (detection bias) AAD	Low risk	Diarrhea assessed by blinded individuals
Incomplete outcome data (attrition bias) CDAD	High risk	"Among the 472 randomized patients, 29 patients were excluded from the ITT analysis due to antibiotic treatment duration of less than 3 days and 6 patients were excluded because diarrhea onset occurred before initiation of study treatment. Therefore a total of 437 (92.6%) were included in the ITT population…" "There were 16 patients in the BIO K+ group and 30 in the placebo group that underwent CDAD testing. Of these, 1 (6.2%) patient in the BIO K+ group and 4 (13.3%) in the placebo group were positive for the *C. difficile* toxins (odds ratio = 0.433, p = 0.645)."

		The missing data results from less than 10% of the participants and the numbers and reasons for those being excluded are balanced across groups. However, a 2:1 difference in sampling for CDAD is apparent and not representative of the difference in occurrence of AAD between groups. Therefore we must conclude a high risk of 'material' bias from incomplete and unbalanced outcome data for the CDAD outcome
Incomplete outcome data (attrition bias) AE	Low risk	The missing data results from less than 10% of the participants and the numbers and reasons for those being excluded are balanced across groups. Therefore we are not concerned about attrition bias as it relates to the AE outcomes
Incomplete outcome data (attrition bias) AAD	Low risk	See above: Incomplete outcome data (attrition bias) AE
Selective reporting (reporting bias)	Low risk	While not reported in the full text article a protocol was discovered on clinicaltrials.gov. The primary outcome listed in the protocol was reported on in the paper. However a secondary outcome listed in the protocol was not mentioned in the paper: "Health outcome evaluation will look at the direct medical costs and clinical outcomes of alternative strategies in the prevention of antibiotic-associated diarrhea in hospitalized adult patients." Additionally, the primary outcome was secondarily analysed using statistical adjustments not prespecified in the protocol. However the unadjusted results are reported as well both in the body and abstract of the paper. We do not consider these concerns sufficient to consider the risk of 'material' reporting bias to be high. We therefore assess the risk of material bias here as low
Other bias	Unclear risk	"The patient demographics and baseline characteristics were similar for the BIO K+ and placebo groups" "John S. Sampalis and Eliofotisti Psaradellis are employees of JSS Medical Research Inc.; JSS Medical Research Inc. was paid by

		BIO K+ International Inc. to conduct and manage this study. JSS Medical Research Inc. was responsible for analyzing and interpreting the data as well as writing and reviewing the manuscript. The study was funded by a grant-in-aid of research from BIO K+ International Inc." Both study authors are employed by a CRO which was paid by the company (Bio K+) which produces the study product

Rafiq 2007

Methods	RCT (control group not stated), follow-up: not stated	
Participants	NS, inpatient, USA, unclear if patients with recurrent *C. difficile* were included	
Interventions	*L. acidophilus* 80%, *L. bulgaricus* 10%, *B. bifidum* 5%, *S. thermophilus* 5%. 3g/day with start of antibiotic until hospital discharge	
Outcomes	CDAD	
Notes	unpublished	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The method of randomization was described
Allocation concealment (selection bias)	Unclear risk	Information not provided
Blinding of participants and personnel (performance bias) CDAD	Unclear risk	No mention of blinding in abstract and multiple contact attempts with author were unsuccessful. While AE were mentioned in abstract results regarding this outcome were not reported so the only relevant outcome for our review is CDAD
Blinding of outcome assessment (detection bias) CDAD	Low risk	There is no mention of blinding of the cytotoxin assay personnel although this is a placebo controlled drug trial so we will consider the risk of bias to be low here

Rafiq 2007 (*Continued*)

Incomplete outcome data (attrition bias) CDAD	Unclear risk	No mention of loss to follow-up in abstract and multiple contact attempts with author were unsuccessful. We are uncertain if there was incomplete outcome data and must assess as unclear
Selective reporting (reporting bias)	Unclear risk	No protocol identified. This is an abstract so unable to determine predefined outcomes from methods section for comparison with results
Other bias	Unclear risk	No information regarding funding is provided. According to our *a priori* defined criteria for RoB assessment we assess this as an unclear risk of bias

Ruszczynski 2008

Methods	Placebo controlled RCT, follow-up: 2 weeks after last study drug
Participants	Pediatric population, mixed inpatient and outpatient, Poland, unclear if patients with recurrent C. diff were included
Interventions	*L. rhamnosus GG* (2593, 2594, 2595) 2 x 10^{10} cfu/day or placebo for duration of antibiotic course
Outcomes	CDAD, AAD, and AE
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The study authors claim to have followed the protocol of an earlier study conducted by their research group (Kotowska 2005). "Investigators at the Medical University of Warsaw used computers to generate independent allocation sequences and randomization lists for each study site. To avoid a disproportionate number of patients in the experimental or placebo group, randomization at each site was performed in blocks of six (three received placebo and three, active treatment)." (Kotowska 2005)

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 of participants and personnel (performance bias) CDAD	Low risk	"This was a double-blind, randomized, placebo-controlled, clinical trial…" "All investigators, participants, outcome assessors and data analysts were blinded to the assigned treatment throughout the study"
Blinding of participants and personnel (performance bias) AE	Low risk	See above: Blinding of participants and personnel (performance bias) CDAD
Blinding of participants and personnel (performance bias) AAD	Low risk	See above: Blinding of participants and personnel (performance bias) CDAD
Blinding of outcome assessment (detection bias) CDAD	Low risk	"All investigators, participants, outcome assessors and data analysts were blinded to the assigned treatment throughout the study"
Blinding of outcome assessment (detection bias) AE	Low risk	See above: Blinding of outcome assessment (detection bias) CDAD
Blinding of outcome assessment (detection bias) AAD	Low risk	See above: Blinding of outcome assessment (detection bias) CDAD
Incomplete outcome data (attrition bias) CDAD	Low risk	"Of the 240 children recruited in the study, we assigned 120 children to receive L. rhamnosus and 120 to receive the placebo. 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 probiotic products. However, no patient was lost to follow-up. Thus, all 240 children enrolled were available for the analysis"
Incomplete outcome data (attrition bias) AE	Low risk	See above: Incomplete outcome data (attrition bias) CDAD
Incomplete outcome data (attrition bias) AAD	Low risk	See above: Incomplete outcome data (attrition bias) CDAD

Ruszczynski 2008 (*Continued*)

Selective reporting (reporting bias)	Low risk	All primary and secondary outcomes were clearly identified in the 'methods' section and analysed in the 'results' section. In addition the study authors claim to have followed the protocol of an earlier study from their group (Kotowska 2005). The outcomes in that earlier paper were identical
Other bias	Low risk	"The study products were supplied by Biomed (Lublin, Poland), who had no role in the conception, design, or conduct of the study or in the analysis or interpretation of the data. Randomization codes were secured until all data entry was complete and data were analysed. The probiotic combination used in this study is commercially available as Lakcid Forte." "Declaration of funding interests: This study was funded in part by Biomed, Lublin, Poland, and the Medical University of Warsaw (Research Agreement UKI 224 2004)." This study appeared free of gross baseline imbalances between groups This study was partially funded by industry but there was a clear declaration of non-involvement and access to study design, conduct etc. According to our *a priori* defined criteria for funding bias we consider this a low risk of 'material' bias

Safdar 2008

Methods	Placebo controlled RCT, follow-up: not stated
Participants	Adult population, inpatient, USA, unclear if patients with recurrent *C. difficile* were included
Interventions	*L. acidophilus* 60 x 10^9 cfu/day or placebo during and 14 days after antibiotic course
Outcomes	CDAD, AAD, and AE
Notes	
Risk of bias	

Safdar 2008 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The method of randomization was not described
Allocation concealment (selection bias)	Unclear risk	Not enough information provided so it is unclear if allocation was successfully concealed
Blinding of participants and personnel (performance bias) CDAD	Low risk	"This was a double-blind randomized placebo-controlled trial…" "Patients and investigators were unaware of treatment assignment"
Blinding of participants and personnel (performance bias) AE	Low risk	See above: Blinding of participants and personnel (performance bias) CDAD
Blinding of participants and personnel (performance bias) AAD	Low risk	See above: Blinding of participants and personnel (performance bias) CDAD
Blinding of outcome assessment (detection bias) CDAD	Low risk	There is no explicit mention of blinding of 'outcome assessors.' There is no mention of blinding of the cytotoxin assay personnel although this is a placebo controlled drug trial so in accordance with our *a priori* defined RoB criteria we will consider the risk of bias to be low here
Blinding of outcome assessment (detection bias) AE	Low risk	It appears AE was assessed by participants reporting to personnel all of whom were blinded
Blinding of outcome assessment (detection bias) AAD	Low risk	It appears diarrhea was assessed by participants reporting to personnel all of whom were blinded
Incomplete outcome data (attrition bias) CDAD	Low risk	"Analyses were intention-to-treat." "Between November 2003 and June 2005, 40 subjects were enrolled and were randomized, 23 to Florajen and 17 to placebo. One subject on placebo withdrew at his request and thus, 23 patients took Florajen and 16 took placebo." "*C. difficile* toxin was obtained only for

		seven patients with diarrhea. It was positive in one and negative in six cases. The one positive case of *C. difficile* diarrhea occurred in a patient randomized to placebo. The six negative cases were evenly distributed in the two study groups." 10 participants developed diarrhea. However only 7 of them were tested for *C. difficile*. Of the three that were not tested 2 were from the placebo group and one was from active group. It seems unlikely to us that this could have led to a 'material' bias that would have affected the authors' conclusions regarding the CDAD outcome. We consider the risk of 'material' bias for the CDAD outcome to be low
Incomplete outcome data (attrition bias) AE	Low risk	"Two subjects in the Florajen group and five in the placebo group reported adverse effects." Analysis was intention-to-treat. It appears one participant withdrew from the study. There was no loss to follow up. We consider the risk of attrition bias for the AE outcome to be low
Incomplete outcome data (attrition bias) AAD	Low risk	"Analyses were intention-to-treat." "Between November 2003 and June 2005, 40 subjects were enrolled and were randomized, 23 to Florajen and 17 to placebo. One subject on placebo withdrew at his request and thus, 23 patients took Florajen and 16 took placebo."
Selective reporting (reporting bias)	Low risk	No protocol for this study was identified. The outcomes listed and described in 'methods' were those analysed in 'results'
Other bias	Unclear risk	This study was free of baseline imbalances. "We thank American Lifeline for providing study medication and placebo." No authors were associated with the company which produces the product being investigated. There is no explicit mention of study funding besides the provision of

		placebo and study medication. According to our *a priori* determined criteria for RoB we consider the lack of adequate funding disclosure to constitute an unclear risk of 'material' bias

Selinger 2011

Methods	Placebo controlled RCT, follow-up: 3 weeks after last study drug dose
Participants	Adult population, inpatient, United Kingdom, unclear if patients with recurrent C. *difficile* were included
Interventions	VSL #3 (*B. breve, B. longum, B. infantis, L. acidophilus, L. plantarum, L. paracasei, L. bulgaricus, S. thermophilus*) 900 x 10^9 cfu/day or placebo during and 7 days after antibiotic course
Outcomes	CDAD, AAD and AE
Notes	interim analysis

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The method of randomization was not described
Allocation concealment (selection bias)	Unclear risk	No relevant information provided
Blinding of participants and personnel (performance bias) CDAD	Low risk	Quote: "This multi-centre, randomised, double-blind, placebo-controlled trial…" Comment: Adequate blinding of participants and personnel. Risk of 'material' performance bias judged to be low
Blinding of participants and personnel (performance bias) AE	Low risk	Quote: "This multi-centre, randomised, double-blind, placebo-controlled trial…" Comment: Adequate blinding of participants and personnel. Risk of 'material' performance bias judged to be low
Blinding of participants and personnel (performance bias) AAD	Low risk	"This multi-centre, randomised, double-blind, placebo-controlled trial…"

Selinger 2011 (*Continued*)

Blinding of outcome assessment (detection bias) CDAD	Low risk	"Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)" Protocol identified on clinicaltrials.gov NCT00973908. Protocol indicated outcome assessors were blinded
Blinding of outcome assessment (detection bias) AE	Low risk	See above: Blinding of outcome assessment (detection bias) CDAD
Blinding of outcome assessment (detection bias) AAD	Low risk	See above: Blinding of outcome assessment (detection bias) CDAD
Incomplete outcome data (attrition bias) CDAD	Low risk	Contact with author was able to provide ITT data. No cases of CDAD were reported in both groups of all randomized participants
Incomplete outcome data (attrition bias) AE	Low risk	See above: Incomplete outcome data (attrition bias) CDAD
Incomplete outcome data (attrition bias) AAD	Low risk	See above: Incomplete outcome data (attrition bias) CDAD
Selective reporting (reporting bias)	Low risk	Protocol identified on clinicaltrials.gov NCT00973908. All outcomes reporting in protocol are reported in analysis of interim abstract
Other bias	Unclear risk	This is an interim analysis of a not fully recruited study. Abstract claims baseline demographics are grossly similar

Shimbo 2005

Methods	No treatment control RCT, follow-up: up to 22 days after starting study drug
Participants	Adult population, outpatients, China, unclear if patients with recurrent *C. difficile* were included
Interventions	Clostridium butyricum MIYAIRI 588, 360 mg/day for 1 week prior to eradication therapy for 14 days
Outcomes	*C. difficile* incidence, AAD and AE
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The method of randomization was not described
Allocation concealment (selection bias)	Unclear risk	No pertinent information provided
Blinding of participants and personnel (performance bias) AE	Unclear risk	"The patients were blindly and randomly allocated to two groups." The study claims the participants were blindly allocated. It is unclear but assumed this refers to blinding of patients to what group they were in. However there was no placebo. The arms were standard therapy versus standard therapy plus probiotics. There is no further explanation as to how the medications were dispensed so it is unclear if blinding could have been assured. Also there is no statement on blinding of study personnel and no mention of double blinding or double dummy. We must assess the risk of 'material' performance bias to be unclear for both *C. difficile* incidence and AE
Blinding of participants and personnel (performance bias) C. difficile incidence	Unclear risk	See above: Blinding of participants and personnel (performance bias) AE
Blinding of participants and personnel (performance bias) AAD	Unclear risk	See above: Blinding of participants and personnel (performance bias) AE
Blinding of outcome assessment (detection bias) AE	Unclear risk	No pertinent information provided
Blinding of outcome assessment (detection bias) C. difficile incidence	Unclear risk	See above: Blinding of outcome assessment (detection bias) AE
Blinding of outcome assessment (detection bias) AAD	Unclear risk	See above: Blinding of outcome assessment (detection bias) AE

Shimbo 2005 (*Continued*)

Incomplete outcome data (attrition bias) AE	Unclear risk	No pertinent information provided
Incomplete outcome data (attrition bias) C. difficile incidence	Unclear risk	See above:Incomplete outcome data (attrition bias) AE
Incomplete outcome data (attrition bias) AAD	Unclear risk	See above:Incomplete outcome data (attrition bias) AE
Selective reporting (reporting bias)	Low risk	No protocol identified. All outcomes discussed in the 'methods' section were analysed in the 'results' section
Other bias	Unclear risk	There is no mention of a funding source. According to our *a priori* determined RoB criteria for funding bias we consider this an unclear risk of 'material' bias

Siitonen 1990

Methods	Placebo controlled RCT, follow-up: last day of treatment
Participants	Adult population, age not stated, Finland, unclear if patients with recurrent *C. difficile* were included
Interventions	LGG yogurt 250 ml/day or placebo for 7 days
Outcomes	AE and *C. difficile* incidence
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The method of randomization was not described
Allocation concealment (selection bias)	Unclear risk	No pertinent information provided and so it is unclear if allocation was successfully concealed
Blinding of participants and personnel (performance bias) AE	Low risk	There is no mention of blinding in this study. However this is a placebo controlled drug trial and so in accordance with our *a priori* determined RoB criteria for performance bias we will consider this as constituting a low risk of 'material' performance

Siitonen 1990 (*Continued*)

		bias
Blinding of participants and personnel (performance bias) C. difficile incidence	Low risk	See above: Blinding of participants and personnel (performance bias) AE
Blinding of outcome assessment (detection bias) AE	Low risk	There is no mention of blinding in this study. However this is a placebo controlled drug trial and so in accordance with our *a priori* determined RoB criteria for detection bias we will consider this as constituting a low risk of 'material' detection bias
Blinding of outcome assessment (detection bias) C. difficile incidence	Low risk	See above: Blinding of outcome assessment (detection bias) AE
Incomplete outcome data (attrition bias) AE	Low risk	It appears there are no missing outcome data
Incomplete outcome data (attrition bias) C. difficile incidence	Low risk	See above: Incomplete outcome data (attrition bias) AE
Selective reporting (reporting bias)	Low risk	A protocol for this study was not identified. Outcomes were not explicitly mentioned as such but all inferred outcomes discussed in 'methods' were reported in 'results'
Other bias	High risk	Four authors are associated with either Valio Finnish Co-operative Dairies' Association or Orion Pharmaceutica. Lactobacillus is an organism found in many fermented dairy products. Orion is an industry that promotes and sells products with Lactobacillus GG which was the study intervention. There is no explicit mention of funding in this trial. However we believe it is likely this study was sponsored by either of the two aforementioned companies. We believe the conflict of interest and likely funding bias makes the risk of 'material' bias high

Sullivan 2004

Methods	Placebo controlled RCT, follow-up: up to 1 month after start of treatment
Participants	Adult population, inpatients, Sweden, unclear if patients with recurrent *C. difficile* were included
Interventions	20 x 10^9 cfu/day *Lactobacillus paracasei spp. paracasei* F19 or placebo for 14 days
Outcomes	*C. difficile* incidence and AE
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The method of randomization was not described
Allocation concealment (selection bias)	Unclear risk	No pertinent information provided so it is unclear if allocation was successfully concealed
Blinding of participants and personnel (performance bias) AE	Low risk	"The two treatment groups were randomized into one placebo and one active group regarding the probiotic supplement in a double-blind fashion." "A similar product was given to patients in the placebo groups but with no added microorganisms"
Blinding of participants and personnel (performance bias) C. difficile incidence	Low risk	See above: Blinding of participants and personnel (performance bias) AE
Blinding of outcome assessment (detection bias) AE	Low risk	It is assumed that AE were reported either by participants to personnel or observed by personnel all of whom where blinded. Therefore, we consider the AE outcome to have been assessed blind
Blinding of outcome assessment (detection bias) C. difficile incidence	Low risk	assay personnel although this is a placebo controlled drug trial so in accordance with our *a priori* determined RoB criteria we will consider the risk of bias to be low here
Incomplete outcome data (attrition bias) AE	High risk	44% of randomized participants did not complete the study and therefore had missing outcome data. This high missing outcome percentage leads us to consider the

Sullivan 2004 (*Continued*)

		risk of 'material' attrition bias to be high for all outcomes
Incomplete outcome data (attrition bias) C. difficile incidence	High risk	See above: Incomplete outcome data (attrition bias) AE
Selective reporting (reporting bias)	Low risk	A protocol of this trial was not located. All outcomes listed in 'methods' were analysed in 'results.' We consider the risk of reporting bias to be low
Other bias	Unclear risk	No financial support, funding, or conflict of interest were listed. According to our *a priori* criteria for risk of funding bias we consider the risk of bias here to be unclear

Surawicz 1989

Methods	Placebo controlled RCT, follow-up: Mean 17.3 days (SD 8.6)
Participants	Adult population, inpatients, USA, unclear if patients with recurrent *C. difficile* were included
Interventions	*S. boulardi* lyophilized 20 x 10^9 cfu/day or placebo within 48 hours of antibiotic commencement until 2 weeks after discontinuation
Outcomes	CDAD, AAD, AE, and *C. difficile* incidence
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The method of randomization was not described
Allocation concealment (selection bias)	Unclear risk	No pertinent information provided and so it is unclear if allocation was successfully concealed
Blinding of participants and personnel (performance bias) CDAD	Low risk	Quotes: "The study was performed double-blindly." "The placebo was an inert composition formulated to be indistinguishable from the capsules of yeast"

Blinding of participants and personnel (performance bias) AE	Low risk	See above: Blinding of participants and personnel (performance bias) CDAD
Blinding of participants and personnel (performance bias) C. difficile incidence	Low risk	See above: Blinding of participants and personnel (performance bias) CDAD
Blinding of participants and personnel (performance bias) AAD	Low risk	See above: Blinding of participants and personnel (performance bias) CDAD
Blinding of outcome assessment (detection bias) CDAD	Low risk	*C. difficile* and the presence of *C. difficile* in those patients with diarrhea (CDAD) were determined via culture and toxin assay laboratory methods. There is no mention of blinding of the laboratory personnel although this is a placebo controlled drug trial so in accordance with our *a priori* defined RoB criteria we will consider the risk of bias to be low here
Blinding of outcome assessment (detection bias) AE	Low risk	While the diarrhea outcome was observed by study personnel as well as reported by participants to study personnel it is unclear how AE were assessed. While we consider this outcome to be a 'subjective' outcome which may be more susceptible to inadequate blinding we assume AE were reported by participants to trial personnel all of whom were blinded. So despite lack of clarity in the reporting of AE outcome assessment and its subjective nature we consider the overall risk of 'material' detection bias for AE to be low
Blinding of outcome assessment (detection bias) C. difficile incidence	Low risk	See above: Blinding of outcome assessment (detection bias) CDAD
Blinding of outcome assessment (detection bias) AAD	Low risk	See above: Blinding of outcome assessment (detection bias) CDAD
Incomplete outcome data (attrition bias) CDAD	High risk	"Of the 318 patients enrolled, 138 could not be evaluated for the following reasons: never received study drug or missed >3 doses (26 patients), developed diarrhea within 24 h of starting study (15 patients)

		or ~72 h of antibiotic therapy (12 patients) , exclusion drug started (9 patients], radiation therapy started (2 patients), or were monitored for <8 days (74 patients)." There is missing outcome data on 43% of randomized participants. This represents a potential for bias especially with the low reported event rate outcomes of CDAD and AE. While some of the missing data appears to have been due to randomized participants not being eligible for the trial due to predefined eligibility criteria there is still a large number of participants with missing outcomes data not due to exclusion criteria. The breakdown of how many missing outcome participants randomized into each group is unclear. Additionally, not all of the 180 evaluated participants were evaluated for C. diff (138 of 180 were). For all of these reasons we consider the risk of 'material' attrition bias to be high in all outcomes
Incomplete outcome data (attrition bias) AE	High risk	See above: Incomplete outcome data (attrition bias) CDAD
Incomplete outcome data (attrition bias) C. difficile incidence	High risk	See above: Incomplete outcome data (attrition bias) CDAD
Incomplete outcome data (attrition bias) AAD	High risk	See above: Incomplete outcome data (attrition bias) CDAD
Selective reporting (reporting bias)	Unclear risk	No protocol identified. "The effectiveness of diarrhea prevention by the yeast was also evaluated in two subgroups of the study population: patients not receiving nasogastric tube feeding and patients infected with *C. difficile*. Patients on nasogastric tube feeding constituted a population with an increased risk of diarrhea (discussed later), and we wanted to evaluate patients in the absence of this risk factor for diarrhea. When patients who received tube feedings were eliminated from the calculations, the rate of diarrhea in the *S. boulardii* group was 5 of 109 (4.6%) compared with 13 of 59 (22%) for placebo

Surawicz 1989 (*Continued*)

		(Figure 1); x2 = 10.42, P < 0.001." 'Outcomes' were not explicitly listed as such in the methods section. Therefore it is difficult to assess whether apparent subgroup analyses such as that evaluating participants with naso-gastric tubes separately constitute "one or more primary outcomes [being] reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified." (Higgins 2011). We therefore consider the risk of 'material' reporting bias to be unclear
Other bias	Low risk	Baseline differences appeared roughly equivalent for the variables analysed "This work was supported by a grant from Laboratoire Biocodex. Montrouge, France. " Sponsor acknowledged but no author is associated with sponsor. According to our *a priori* determined criteria for RoB assessment we consider the risk of 'material' bias to be low here

Thomas 2001

Methods	Placebo controlled RCT, follow-up: 7 days after last study drug dose
Participants	Adult population, inpatient, USA, 2 patients in group 1 and 3 in the control group had a history of *C. difficile* infection
Interventions	*L. rhamnosus GG* 20 x 10^9 cfu/day or placebo within 24 hours of antibiotic commencement then for 14 days
Outcomes	CDAD, AAD and AE
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"A randomization schedule was generated by the Section of Biostatistics and stratified on 3 parameters, including baseline daily bowel movement frequency (<1 vs >1), use

		of beta-lactams as initial antibiotic therapy, and age at entry (<65 vs >65 years)." While the exact mechanism of randomization is not described we consider the involvement of the biostatistics department to be sufficient to assume a low risk of 'material' selection bias due to inadequate sequence generation
Allocation concealment (selection bias)	Low risk	"A pharmacist who at no time had direct contact with the patients or investigators dispensed active and placebo capsules according to the randomization schedule"
Blinding of participants and personnel (performance bias) CDAD	Low risk	Quotes: "Patients and investigators were blinded to the treatment." "Placebo capsules appeared identical to the active capsules..."
Blinding of participants and personnel (performance bias) AE	Low risk	See above: Blinding of participants and personnel (performance bias) CDAD
Blinding of participants and personnel (performance bias) AAD	Low risk	See above: Blinding of participants and personnel (performance bias) CDAD
Blinding of outcome assessment (detection bias) CDAD	Low risk	It appears that CDAD was determined by following up with the participants' primary care physicians and comparing hospital records of *C. difficile* positive patients which those enrolled in the trial. While it is not completely clear it seems as though the trial personnel were not those involved in assessing *C. difficile* but rather that those managing the patients ordered the tests themselves. Although this is unclear, this is a placebo controlled drug trial which is described as double blind. Based on our *a priori* determined criteria for the risk of bias for outcome assessor blinding this is sufficient to assess the risk of 'material' bias to be low here
Blinding of outcome assessment (detection bias) AE	Low risk	It appears AE was reported by participants to study personnel all of whom were blinded

Blinding of outcome assessment (detection bias) AAD	Low risk	It appears AAD was reported by blinded individuals
Incomplete outcome data (attrition bias) CDAD	Low risk	"Of the 302 patients who consented to participate, 34 failed to complete the study, and 1 patient enrolled but discontinued antibiotics after 1 dose, so was therefore determined to be ineligible. Thus, 267 patients completed the study." 12% missing data. The placebo group had 16 participants withdrawn (Dropped out (n=9), Insufficient follow-up (n=7)) and the treatment group had 19 participants withdrawn (Dropped out (n=14), Insufficient follow-up (n=4), Discontinued antibiotic after 1 dose (n=1)) The numbers of missing data are grossly even between groups and not extreme. The reasons for withdrawal and dropout are not described "A chart review and a list of all patients with a positive *C difficile* toxin assay since July 1998 obtained from the Mayo Clinic microbiology laboratory revealed 5 study patients diagnosed as having and treated for *C difficile* colitis at our institution. Two of these patients were randomized to *Lactobacillus* GG, and 3 were randomized to placebo." The chart review displayed infrequent CDAD and seemingly same frequency in both groups. While the reasons for withdrawal and drop out were not clear, in light of the authors' negative findings we elected not to rate down here
Incomplete outcome data (attrition bias) AE	Unclear risk	"There was no difference in the proportion of patients experiencing nausea or abdominal cramping between the groups (P=.40 and P=.74, respectively). The patients receiving placebo tended to report gas or bloating more often than those receiving *Lactobacillus* GG (38.8% vs 28.0%), but this difference was not statistically significant (P=.06)."

		Numbers of patients from each group experiencing the AE of nausea and abdominal cramping cannot be calculated from the presented data. The event rates for gas and bloating can be calculated and the event rates are frequent enough to most likely not be significantly influenced by the relatively low amount of missing data. However, not all event rates are clear and so it is difficult to assess the risk of attrition bias in this instance
Incomplete outcome data (attrition bias) AAD	Unclear risk	The numbers of missing data are grossly even between groups and not extreme. The reasons for withdrawal and dropout are not described
Selective reporting (reporting bias)	Low risk	"The primary outcome was the proportion of patients experiencing diarrhea in the first 21 days after enrollment." "Two secondary outcomes were also assessed. The first was the proportion of patients who had either stool cultures or additional testing to determine the cause of diarrhea in the first 21 days after enrollment. These tests included fecal leukocyte counts, stool osmolality, and stool electrolytes. The second assessment was to determine the number of patients who were diagnosed as having AAD due to *C difficile* in the first 21 days or at any time after enrollment." Despite the clear declaration of outcomes in the 'methods' section the primary outcome was assessed with multiple subgroup analyses not discussed in 'methods.' Examples include subgroups based on type of antibiotic, differing definitions of diarrhea, duration of antibiotic treatment, severe diarrhea and length of hospitalization. Therefore the primary outcome of rate of diarrhea was "reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified". This classifies as a high risk of bias (Higgins 2011). This being said it is important to note that none of the subgroups resulted in

		significant findings either so this concern would be unlikely to bias the authors' conclusion. Considering the authors' conclusions, the direction of expected bias, and that these subgroups were not pertinent to our review, we consider the risk of a 'material' reporting bias that could influence our cumulative effect estimate in meta-analysis to be low
Other bias	Low risk	"The treatment (n=133) and placebo (n=134) groups were similar in terms of their demographics and medical profiles at enrollment." The study appears free of baseline imbalances "This study was supported in part by a grant from ConAgra Foods, Inc, Omaha, Neb." "Active capsules (CAG Functional Foods, Omaha, Neb)…" The study product is produced by a division of the sponsoring company (ConAgra). The sponsor is acknowledged and no one from the sponsoring agency was an author so based on our *a priori* defined criteria for funding bias we consider the risk of 'material' bias to be low

Wenus 2008

Methods	Placebo controlled RCT
Participants	Adult population, NS, Norway, unclear if patients with recurrent *C. difficile* were included
Interventions	Mixture of LGG, Lactobacillus acidophilus, and bifidobacterium 52.5 x 10^9 cfu/day or placebo for 14 days
Outcomes	CDAD, AAD and *C. difficile* incidence
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The method of randomization was not described

Wenus 2008 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	No pertinent information provided and so it is unclear if allocation was successfully concealed
Blinding of participants and personnel (performance bias) CDAD	Low risk	"In this double-blind placebo controlled study…" "Both products had a neutral taste…"
Blinding of participants and personnel (performance bias) C. difficile incidence	Low risk	See above: Blinding of participants and personnel (performance bias) CDAD
Blinding of participants and personnel (performance bias) AAD	Low risk	See above: Blinding of participants and personnel (performance bias) CDAD
Blinding of outcome assessment (detection bias) CDAD	Low risk	There is no mention of blinding of the cytotoxin assay personnel although this is a placebo controlled drug trial so in accordance with our *a priori* defined RoB criteria we will consider the risk of bias to be low here
Blinding of outcome assessment (detection bias) C. difficile incidence	Low risk	See above: Blinding of outcome assessment (detection bias) CDAD
Blinding of outcome assessment (detection bias) AAD	Low risk	Diarrhea assessed by participants who were blinded
Incomplete outcome data (attrition bias) CDAD	High risk	"The remaining 87 intention-to-treat patients were randomized to probiotic (n = 46) or placebo (n = 41) treatment. Groups were well balanced at study entry (Table 1). During the study there were 12 withdrawals/drop-outs in each treatment group (Figure 1). The remaining 34 and 29 patients in the active and placebo group, respectively, completed the study according to the protocol. The withdrawal/drop-out group did not differ from the per-protocol group with respect to age, sex, usual number of stools/day and previous experiences of AAD (data not shown) "Stool samples were collected twice during the study period. " "Owing to low patient compliance, only 55 stool samples were examined. In the non-AAD/probiotic group one sample was positive for *C. difficile* culture, and another sample was positive for *C. difficile* toxin A. In the AAD/placebo group one sample was positive for *C. difficile* culture"

		"Our study was based on per-protocol analysis. Intention-to-treat analysis could not be obtained as end point data was lacking for several patients owing to withdrawal or drop-out. " Comment: There are missing outcome data on 28% of randomized participants. Additionally it appears that of the remaining 63 participants there should have been 126 stool samples for *C. difficile* analysis. Only 55 were analysed. These concerns coupled with an extremely low *C. difficile* incidence event rate lead us to consider the risk of 'material' attrition bias to be high
Incomplete outcome data (attrition bias) C. difficile incidence	High risk	See above: Incomplete outcome data (attrition bias) CDAD
Incomplete outcome data (attrition bias) AAD	High risk	See above: Incomplete outcome data (attrition bias) CDAD
Selective reporting (reporting bias)	Low risk	No protocol for this study was identified. All outcomes listed in the 'methods' section were analysed in the 'results' section
Other bias	Low risk	Groups apparently free of baseline imbalances. The investigated product is produced by the sponsor of this trial (Biola: TINE BA, Oslo, Norway). No author was associated with the sponsoring company

Methods: Randomized controlled trial (RCT)
Interventions: Colony-forming units (cfu)
Outcomes: Clostridium difficile-associated diarrhea (CDAD), antibiotic-associated diarrhea (AAD), adverse events (AE)

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

Study	Reason for exclusion
Agarwal 2003	*C. difficile* or CDAD not measured
Allen 2012	Not an RCT
Anukam 2006	*C. difficile* or CDAD not measured
Armuzzi 2001	*C. difficile* or CDAD not measured
Avadhani 2011	Not an RCT

(*Continued*)

Basu 2007	*C. difficile* or CDAD not measured
Bekar 2011	*C. difficile* or CDAD not measured
Bellomo 1980	*C. difficile* or CDAD not measured
Benhamou 1999	*C. difficile* or CDAD not measured
Beniwal 2003	*C. difficile* or CDAD not measured
Berni 2011	Not an RCT
Black 1991	*C. difficile* or CDAD not measured
Bleichner 1997	*C. difficile* or CDAD not measured
Brunser 2006	*C. difficile* or CDAD not measured
Butler 2012	Not an RCT
Chapman 2011	Not an RCT
Chen 2011	Not an RCT
Cimperman 2011	*C. difficile* or CDAD not measured
Clements 1981	*C. difficile* or CDAD not measured
Contardi 1991	*C. difficile* or CDAD not measured
Conway 2007	*C. difficile* or CDAD not measured
Correa 2005	*C. difficile* or CDAD not measured
Cremonini 2002	*C. difficile* or CDAD not measured
de Bortoli 2007	*C. difficile* or CDAD not measured
de Vrese 2011	*C. difficile* or CDAD not measured
Elmer 1999	Patients had active diarrhea or CDAD
Erdeve 2004	*C. difficile* or CDAD not measured
Felley 2001	*C. difficile* or CDAD not measured
Forestier 2008	*C. difficile* or CDAD not measured

(*Continued*)

Francavilla 2008	*C. difficile* or CDAD not measured
Goldman 2006	*C. difficile* or CDAD not measured
Gotteland 2005	*C. difficile* or CDAD not measured
Gotz 1979	*C. difficile* or CDAD not measured
Guandalini 2000	*C. difficile* or CDAD not measured
Hafeez 2002	*C. difficile* or CDAD not measured
Hatakka 2001	*C. difficile* or CDAD not measured
Heimburger 1994	*C. difficile* or CDAD not measured
Hotz 1990	*C. difficile* or CDAD not measured
Hurduc 2009	*C. difficile* or CDAD not measured
Jacobi 2011	Not an RCT
Jirapinyo 2002	*C. difficile* or CDAD not measured
Kato 2004	*C. difficile* or CDAD not measured
Kollaritsch 1993	*C. difficile* or CDAD not measured
Kruis 2012	*C. difficile* or CDAD not measured
La Rosa 2003	*C. difficile* or CDAD not measured
Lawrence 2005	Patients had active diarrhea or CDAD
Lei 2006	*C. difficile* or CDAD not measured
Lionetti 2006	*C. difficile* or CDAD not measured
Madden 2005	*C. difficile* or CDAD not measured
Madeo 1999	*C. difficile* or CDAD not measured
Marcone 2008	*C. difficile* or CDAD not measured
Marshall 2008	Not an RCT
Martinez 2009	*C. difficile* or CDAD not measured

(*Continued*)

McFarland 1994a	Patients had active diarrhea or CDAD
Merenstein 2009	*C. difficile* or CDAD not measured
Mihatsch 2010	*C. difficile* or CDAD not measured
Mohan 2008	*C. difficile* or CDAD not measured
Myllyluoma 2005	*C. difficile* or CDAD not measured
Myllyluoma 2007	*C. difficile* or CDAD not measured
Nista 2004	*C. difficile* or CDAD not measured
Oleinichenko 1999	*C. difficile* or CDAD not measured
Ozdil 2011	*C. difficile* or CDAD not measured
Park 2007	*C. difficile* or CDAD not measured
Pereg 2005	*C. difficile* or CDAD not measured
Pirotta 2004	*C. difficile* or CDAD not measured
Plewinska 2006	*C. difficile* or CDAD not measured
Pochapin 2000	Patients had active diarrhea or CDAD
Potts 1996	*C. difficile* or CDAD not measured
Pushkarev 2005	*C. difficile* or CDAD not measured
Ranasinghe 2007	*C. difficile* or CDAD not measured
Rayes 2002a	*C. difficile* or CDAD not measured
Rayes 2002b	*C. difficile* or CDAD not measured
Rayes 2002c	*C. difficile* or CDAD not measured
Reddy 2007	*C. difficile* or CDAD not measured
Robertson 2000	Not an RCT
Sahagún-Flores 2007	*C. difficile* or CDAD not measured
Schrezenmeir 2002	*C. difficile* or CDAD not measured

(*Continued*)

Schrezenmeir 2004	*C. difficile* or CDAD not measured
Sepp 2011	Not an RCT
Souza 2012	*C. difficile* or CDAD not measured
Stein 2007	*C. difficile* or CDAD not measured
Stockenhuber 2008	Not an RCT
Tankanow 1990	*C. difficile* or CDAD not measured
Tursi 2004	*C. difficile* or CDAD not measured
Vandenplas 2011	*C. difficile* or CDAD not measured
Wilhelm 2011	Not an RCT
Witsell 1995	*C. difficile* or CDAD not measured
Woo 2008	Not an RCT
Wullt 2007	Patients had active diarrhea or CDAD
Yoon 2011	*C. difficile* or CDAD not measured
Yost 1985	*C. difficile* or CDAD not measured
Ziemniak 2006	*C. difficile* or CDAD not measured

DATA AND ANALYSES

Comparison 1. C. difficile associated diarrhea

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence CDAD: complete case	23	4213	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.26, 0.51]
2 Incidence CDAD: complete case - fixed effects	23	4213	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.26, 0.49]
3 Incidence CDAD Sensitivity (1.5:1)	23	4674	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.27, 0.53]
4 Incidence CDAD Sensitivity (2:1)	23	4674	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.30, 0.57]
5 Incidence CDAD Sensitivity (3:1)	23	4674	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.33, 0.68]
6 Incidence CDAD Sensitivity (5:1)	23	4674	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.38, 0.85]
7 Incidence CDAD: Subgroup: Inpatient versus outpatient populations	21	4026	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.26, 0.52]
7.1 Inpatient	14	2359	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.24, 0.52]
7.2 Outpatient	2	462	Risk Ratio (M-H, Random, 95% CI)	0.31 [0.01, 7.47]
7.3 Mixed	5	1205	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.20, 0.94]
8 Incidence CDAD: Subgroup: Species: all	22	4156	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.26, 0.51]
8.1 Lactobacillus GG	5	1131	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.30, 1.33]
8.2 S. boulardii	7	1507	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.24, 0.94]
8.3 L. acidophilus + L. casei	3	781	Risk Ratio (M-H, Random, 95% CI)	0.21 [0.11, 0.42]
8.4 L. acidophilus + B. bifidum	1	138	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.08, 1.99]
8.5 L. acidophilus	1	40	Risk Ratio (M-H, Random, 95% CI)	0.25 [0.01, 5.79]
8.6 L. acidophilus + L. bulgaricus + B. bifidum + S. thermophilus	1	100	Risk Ratio (M-H, Random, 95% CI)	0.28 [0.11, 0.67]
8.7 B. breve + B. Longum + B. infantis + L. acidophilus + L. plantarum + L. paracasei + L. bulgaricus + S. thermophilus	1	124	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
8.8 L. casei + L. bulgaris + S. thermophilus	1	109	Risk Ratio (M-H, Random, 95% CI)	0.05 [0.00, 0.84]
8.9 L. plantarum	1	163	Risk Ratio (M-H, Random, 95% CI)	3.11 [0.13, 75.26]
8.10 Lactobacillus GG + L. acidophilus + B. animalis	1	63	Risk Ratio (M-H, Random, 95% CI)	0.29 [0.01, 6.76]
9 Incidence CDAD: Subgroup: Species: LGG versus SB	12	2638	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.33, 0.90]
9.1 Lactobacillus GG	5	1131	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.30, 1.33]
9.2 S. boulardii	7	1507	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.24, 0.94]

10 Incidence CDAD: Subgroup: Species: LGG versus LA + LC	8	1912	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.21, 0.57]
10.1 Lactobacillus GG	5	1131	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.30, 1.33]
10.2 L. acidophilus + L. casei	3	781	Risk Ratio (M-H, Random, 95% CI)	0.21 [0.11, 0.42]
11 Incidence CDAD: Subgroup: Risk of Bias	23	4280	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.26, 0.51]
11.1 Low risk of bias	7	1308	Risk Ratio (M-H, Random, 95% CI)	0.27 [0.16, 0.46]
11.2 High or unclear risk of bias	16	2972	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.28, 0.72]
12 Incidence CDAD: Subgroup: Adult versus child	22	4156	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.26, 0.51]
12.1 Adult studies	19	3551	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.24, 0.52]
12.2 Pediatric studies	3	605	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.17, 0.96]

Comparison 2. Adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Adverse Events: complete case	26	3964	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.68, 0.95]
2 Adverse Events: Subgroup: Risk of Bias	26	4031	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.68, 0.95]
2.1 Low Risk of Bias	12	2120	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.72, 0.98]
2.2 High/Unclear risk of bias	14	1911	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.29, 0.99]
3 AE Sensitivity 1.5:1	26	4468	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.69, 0.99]
4 AE Sensitivity 2:1	26	4468	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.70, 1.03]
5 AE Sensitivity 3:1	26	4468	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.70, 1.10]
6 AE Sensitivity 5:1	26	4468	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.72, 1.21]

Comparison 3. Incidence of Clostridium difficile infection

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of infection: complete case	13	961	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.64, 1.24]
2 Incidence of infection: Subgroup: Risk of Bias	13	961	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.64, 1.24]
2.1 Low Risk of Bias	3	130	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.31, 2.20]
2.2 High or Unclear Risk of Bias	10	831	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.63, 1.28]

Comparison 4. Length of hospital stay

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Length of Hospital Stay: complete case	3	422	Mean Difference (IV, Random, 95% CI)	-0.32 [-3.21, 2.57]

Comparison 5. Antibiotic associated diarrhea

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence AAD: complete case	25	4097	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.49, 0.72]
2 Incidence AAD: Subgroup: Risk of Bias	25	4097	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.49, 0.72]
2.1 Low risk of bias	13	2154	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.46, 0.73]
2.2 High or Unclear risk of bias	12	1943	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.44, 0.88]
3 Incidence AAD: sensitivity (1.5:1)	25	4581	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.58, 0.82]
4 Incidence AAD: sensitivity (2:1)	25	4581	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.60, 0.88]
5 Incidence AAD: sensitivity (3:1)	25	4581	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.64, 0.99]
6 Incidence AAD: sensitivity (5:1)	25	4581	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.69, 1.18]
7 Patient population	21	3853	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.50, 0.76]
7.1 Inpatient	13	2138	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.49, 0.88]
7.2 Outpatient	3	510	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.30, 0.87]
7.3 Mixed	5	1205	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.35, 0.86]
8 Species: all	25	4097	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.49, 0.72]
8.1 Lactobacillus GG	4	942	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.39, 1.43]
8.2 S. boulardi	9	1642	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.39, 0.80]
8.3 L. acidophilus + L. casei	3	781	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.42, 0.81]
8.4 Clostridium butyricum	2	54	Risk Ratio (M-H, Random, 95% CI)	0.29 [0.06, 1.34]
8.5 L. acidophilus + B. bifidum	1	138	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.51, 1.36]
8.6 L. acidophilus	1	39	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.16, 1.38]
8.7 B. breve + B. longum + B. infantis + L. acidophilus + L. plantarum	1	124	Risk Ratio (M-H, Random, 95% CI)	0.4 [0.08, 1.98]
8.8 L. casei + L. bulgaris + S. thermophilus	1	113	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.17, 0.79]
8.9 L. plantarum	1	163	Risk Ratio (M-H, Random, 95% CI)	1.25 [0.40, 3.92]
8.10 Lactobacillus GG + L. acidophilus + B. animalis	1	63	Risk Ratio (M-H, Random, 95% CI)	0.21 [0.05, 0.93]

8.11 B. bifidum + B. lactis + B. longum + E. faecium + L. acidophilus + L. paracasei + L. plantarum + L. rhamnosus + L. sativarius	1	38	Risk Ratio (M-H, Random, 95% CI)	0.6 [0.35, 1.02]
9 Species: LGG versus SB	13	2584	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.45, 0.86]
9.1 LGG	4	942	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.39, 1.43]
9.2 SB	9	1642	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.39, 0.80]
10 Species: LGG versus LA + LC	7	1723	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.47, 0.91]
10.1 LGG	4	942	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.39, 1.43]
10.2 LA + LC	3	781	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.42, 0.81]
11 Adult versus child	22	3974	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.49, 0.71]
11.1 Adult	19	3369	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.51, 0.76]
11.2 Child	3	605	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.23, 0.60]

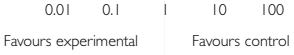
Analysis 1.1. Comparison 1 C. difficile associated diarrhea, Outcome 1 Incidence CDAD: complete case.

Review: Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children

Comparison: 1 C. difficile associated diarrhea

Outcome: 1 Incidence CDAD: complete case

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Arvola 1999	1/61	1/58		1.6 %	0.95 [0.06, 14.85]
Beausoleil 2007	1/44	7/45		2.9 %	0.15 [0.02, 1.14]
Bravo 2008	0/41	0/45			Not estimable
Can 2006	0/73	2/78		1.3 %	0.21 [0.01, 4.37]
Cindoruk 2007	0/62	0/62			Not estimable
Duman 2005	0/196	1/180		1.2 %	0.31 [0.01, 7.47]
Gao 2010	9/171	20/84		21.9 %	0.22 [0.11, 0.46]
Hickson 2007	0/57	9/56		1.5 %	0.05 [0.00, 0.87]
Kotowska 2005	3/119	10/127		7.5 %	0.32 [0.09, 1.14]
Lonnermark 2010	1/80	0/83		1.2 %	3.11 [0.13, 75.26]
McFarland 1995	3/97	4/96		5.6 %	0.74 [0.17, 3.23]
Miller 2008a	4/95	7/94		8.4 %	0.57 [0.17, 1.87]
Miller 2008b	2/157	0/159		1.3 %	5.06 [0.25, 104.63]
Plummer 2004	2/69	5/69		4.7 %	0.40 [0.08, 1.99]



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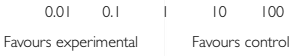
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Pozzoni 2012	3/106	2/98		3.9 %	1.39 [0.24, 8.13]
Psaradellis 2010	1/216	4/221		2.5 %	0.26 [0.03, 2.27]
Rafiq 2007	5/45	22/55		15.3 %	0.28 [0.11, 0.67]
Ruszczynski 2008	3/120	7/120		6.8 %	0.43 [0.11, 1.62]
Safdar 2008	0/23	1/17		1.2 %	0.25 [0.01, 5.79]
Selinger 2011	0/62	0/62			Not estimable
Surawicz 1989	3/116	5/64		6.2 %	0.33 [0.08, 1.34]
Thomas 2001	2/133	3/134		3.8 %	0.67 [0.11, 3.96]
Wenus 2008	0/34	1/29		1.2 %	0.29 [0.01, 6.76]
Total (95% CI)	**2177**	**2036**		**100.0 %**	**0.36 [0.26, 0.51]**

Total events: 43 (Experimental), 111 (Control)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 14.33$, df = 19 (P = 0.76); $I^2 = 0.0\%$

Test for overall effect: Z = 5.73 (P < 0.00001)

Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1 C. difficile associated diarrhea, Outcome 2 Incidence CDAD: complete case - fixed effects.

Review: Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children

Comparison: 1 C. difficile associated diarrhea

Outcome: 2 Incidence CDAD: complete case - fixed effects

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Arvola 1999	1/61	1/58		0.8 %	0.95 [0.06, 14.85]
Beausoleil 2007	1/44	7/45		5.7 %	0.15 [0.02, 1.14]
Bravo 2008	0/41	0/45			Not estimable
Can 2006	0/73	2/78		2.0 %	0.21 [0.01, 4.37]
Cindoruk 2007	0/62	0/62			Not estimable
Duman 2005	0/196	1/180		1.3 %	0.31 [0.01, 7.47]
Gao 2010	9/171	20/84		22.2 %	0.22 [0.11, 0.46]
Hickson 2007	0/57	9/56		7.9 %	0.05 [0.00, 0.87]
Kotowska 2005	3/119	10/127		8.0 %	0.32 [0.09, 1.14]
Lonnermark 2010	1/80	0/83		0.4 %	3.11 [0.13, 75.26]
McFarland 1995	3/97	4/96		3.3 %	0.74 [0.17, 3.23]
Miller 2008a	4/95	7/94		5.8 %	0.57 [0.17, 1.87]
Miller 2008b	2/157	0/159		0.4 %	5.06 [0.25, 104.63]
Plummer 2004	2/69	5/69		4.1 %	0.40 [0.08, 1.99]
Pozzoni 2012	3/106	2/98		1.7 %	1.39 [0.24, 8.13]
Psaradellis 2010	1/216	4/221		3.3 %	0.26 [0.03, 2.27]
Rafiq 2007	5/45	22/55		16.4 %	0.28 [0.11, 0.67]
Ruszczynski 2008	3/120	7/120		5.8 %	0.43 [0.11, 1.62]
Safdar 2008	0/23	1/17		1.4 %	0.25 [0.01, 5.79]
Selinger 2011	0/62	0/62			Not estimable
Surawicz 1989	3/116	5/64		5.3 %	0.33 [0.08, 1.34]
Thomas 2001	2/133	3/134		2.5 %	0.67 [0.11, 3.96]
Wenus 2008	0/34	1/29		1.3 %	0.29 [0.01, 6.76]
Total (95% CI)	**2177**	**2036**		**100.0 %**	**0.36 [0.26, 0.49]**

Total events: 43 (Experimental), 111 (Control)

Heterogeneity: Chi^2 = 14.33, df = 19 (P = 0.76); I^2 =0.0%

Test for overall effect: Z = 6.15 (P < 0.00001)

Test for subgroup differences: Not applicable

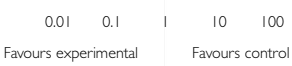
Analysis 1.3. Comparison 1 C. difficile associated diarrhea, Outcome 3 Incidence CDAD Sensitivity (1.5:1).

Review: Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children

Comparison: 1 C. difficile associated diarrhea

Outcome: 3 Incidence CDAD Sensitivity (1.5:1)

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Arvola 1999	2/89	1/78		1.9 %	1.75 [0.16, 18.96]
Beausoleil 2007	1/44	7/45		2.5 %	0.15 [0.02, 1.14]
Bravo 2008	0/41	0/45			Not estimable
Can 2006	0/73	2/78		1.2 %	0.21 [0.01, 4.37]
Cindoruk 2007	0/62	1/62		1.0 %	0.33 [0.01, 8.03]
Duman 2005	0/204	1/185		1.0 %	0.30 [0.01, 7.38]
Gao 2010	9/171	20/84		19.1 %	0.22 [0.11, 0.46]
Hickson 2007	0/69	11/66		1.3 %	0.04 [0.00, 0.69]
Kotowska 2005	3/132	11/137		6.7 %	0.28 [0.08, 0.99]
Lonnermark 2010	2/118	0/121		1.2 %	5.13 [0.25, 105.66]
McFarland 1995	4/97	5/96		6.4 %	0.79 [0.22, 2.86]
Miller 2008a	4/95	7/94		7.4 %	0.57 [0.17, 1.87]
Miller 2008b	2/157	0/159		1.1 %	5.06 [0.25, 104.63]
Plummer 2004	2/69	5/69		4.1 %	0.40 [0.08, 1.99]
Pozzoni 2012	4/141	4/134		5.7 %	0.95 [0.24, 3.72]
Psaradellis 2010	1/233	5/239		2.3 %	0.21 [0.02, 1.74]
Rafiq 2007	5/45	22/55		13.4 %	0.28 [0.11, 0.67]
Ruszczynski 2008	3/120	7/120		6.0 %	0.43 [0.11, 1.62]
Safdar 2008	0/23	1/17		1.1 %	0.25 [0.01, 5.79]
Selinger 2011	0/62	0/62			Not estimable
Surawicz 1989	7/212	9/106		11.4 %	0.39 [0.15, 1.02]
Thomas 2001	2/152	3/150		3.3 %	0.66 [0.11, 3.88]



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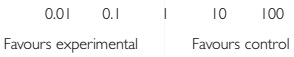
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Wenus 2008	1/34	2/29		1.9 %	0.43 [0.04, 4.47]
Total (95% CI)	**2443**	**2231**		**100.0 %**	**0.38 [0.27, 0.53]**

Total events: 52 (Experimental), 124 (Control)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 17.58$, df = 20 (P = 0.61); $I^2 = 0.0\%$

Test for overall effect: Z = 5.84 (P < 0.00001)

Test for subgroup differences: Not applicable



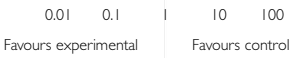
Analysis 1.4. Comparison 1 C. difficile associated diarrhea, Outcome 4 Incidence CDAD Sensitivity (2:1).

Review: Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children

Comparison: 1 C. difficile associated diarrhea

Outcome: 4 Incidence CDAD Sensitivity (2:1)

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Arvola 1999	2/89	1/78		1.8 %	1.75 [0.16, 18.96]
Beausoleil 2007	1/44	7/45		2.4 %	0.15 [0.02, 1.14]
Bravo 2008	0/41	0/45			Not estimable
Can 2006	0/73	2/78		1.1 %	0.21 [0.01, 4.37]
Cindoruk 2007	0/62	1/62		1.0 %	0.33 [0.01, 8.03]
Duman 2005	0/204	1/185		1.0 %	0.30 [0.01, 7.38]
Gao 2010	9/171	20/84		18.5 %	0.22 [0.11, 0.46]
Hickson 2007	0/69	11/66		1.3 %	0.04 [0.00, 0.69]
Kotowska 2005	4/132	11/137		8.1 %	0.38 [0.12, 1.16]
Lonnermark 2010	2/118	0/121		1.1 %	5.13 [0.25, 105.66]
McFarland 1995	4/97	5/96		6.2 %	0.79 [0.22, 2.86]



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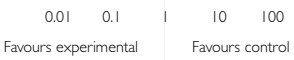
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Miller 2008a	4/95	7/94		7.1 %	0.57 [0.17, 1.87]
Miller 2008b	2/157	0/159		1.1 %	5.06 [0.25, 104.63]
Plummer 2004	2/69	5/69		3.9 %	0.40 [0.08, 1.99]
Pozzoni 2012	5/141	4/134		6.1 %	1.19 [0.33, 4.33]
Psaradellis 2010	1/233	5/239		2.2 %	0.21 [0.02, 1.74]
Rafiq 2007	5/45	22/55		12.9 %	0.28 [0.11, 0.67]
Ruszczynski 2008	3/120	7/120		5.8 %	0.43 [0.11, 1.62]
Safdar 2008	0/23	1/17		1.0 %	0.25 [0.01, 5.79]
Selinger 2011	0/62	0/62			Not estimable
Surawicz 1989	8/212	9/106		11.9 %	0.44 [0.18, 1.12]
Thomas 2001	3/152	3/150		4.1 %	0.99 [0.20, 4.81]
Wenus 2008	1/34	1/29		1.4 %	0.85 [0.06, 13.04]
Total (95% CI)	**2443**	**2231**		**100.0 %**	**0.41 [0.30, 0.57]**

Total events: 56 (Experimental), 123 (Control)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 19.83$, df = 20 (P = 0.47); $I^2 = 0.0\%$

Test for overall effect: Z = 5.43 (P < 0.00001)

Test for subgroup differences: Not applicable



Analysis 1.5. Comparison 1 C. difficile associated diarrhea, Outcome 5 Incidence CDAD Sensitivity (3:1).

Review: Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children

Comparison: 1 C. difficile associated diarrhea

Outcome: 5 Incidence CDAD Sensitivity (3:1)

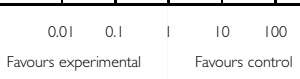
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Arvola 1999	2/89	1/78		2.1 %	1.75 [0.16, 18.96]
Beausoleil 2007	1/44	7/45		2.7 %	0.15 [0.02, 1.14]
Bravo 2008	0/41	0/45			Not estimable
Can 2006	0/73	2/78		1.3 %	0.21 [0.01, 4.37]
Cindoruk 2007	0/62	1/62		1.2 %	0.33 [0.01, 8.03]
Duman 2005	0/204	1/185		1.2 %	0.30 [0.01, 7.38]
Gao 2010	9/171	20/84		14.2 %	0.22 [0.11, 0.46]
Hickson 2007	0/69	11/66		1.5 %	0.04 [0.00, 0.69]
Kotowska 2005	4/132	11/137		7.9 %	0.38 [0.12, 1.16]
Lonnermark 2010	3/118	0/121		1.4 %	7.18 [0.37, 137.44]
McFarland 1995	5/97	5/96		7.0 %	0.99 [0.30, 3.31]
Miller 2008a	4/95	7/94		7.1 %	0.57 [0.17, 1.87]
Miller 2008b	2/157	0/159		1.3 %	5.06 [0.25, 104.63]
Plummer 2004	2/69	5/69		4.3 %	0.40 [0.08, 1.99]
Pozzoni 2012	6/141	4/134		6.6 %	1.43 [0.41, 4.94]
Psaradellis 2010	2/233	5/239		4.2 %	0.41 [0.08, 2.09]
Rafiq 2007	5/45	22/55		11.2 %	0.28 [0.11, 0.67]
Ruszczynski 2008	3/120	7/120		5.9 %	0.43 [0.11, 1.62]
Safdar 2008	0/23	1/17		1.2 %	0.25 [0.01, 5.79]
Selinger 2011	0/62	0/62			Not estimable
Surawicz 1989	11/212	9/106		11.9 %	0.61 [0.26, 1.43]
Thomas 2001	3/152	3/150		4.4 %	0.99 [0.20, 4.81]
Wenus 2008	1/34	1/29		1.6 %	0.85 [0.06, 13.04]
Total (95% CI)	**2443**	**2231**		**100.0 %**	**0.47 [0.33, 0.68]**

Total events: 63 (Experimental), 123 (Control)

Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 23.00$, df = 20 (P = 0.29); $I^2 = 13\%$

Test for overall effect: Z = 4.15 (P = 0.000033)

Test for subgroup differences: Not applicable



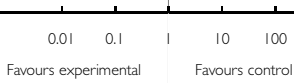
Analysis 1.6. Comparison 1 C. difficile associated diarrhea, Outcome 6 Incidence CDAD Sensitivity (5:1).

Review: Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children

Comparison: 1 C. difficile associated diarrhea

Outcome: 6 Incidence CDAD Sensitivity (5:1)

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Arvola 1999	3/89	1/78		2.7 %	2.63 [0.28, 24.76]
Beausoleil 2007	2/44	7/45		5.0 %	0.29 [0.06, 1.33]
Bravo 2008	0/41	0/45			Not estimable
Can 2006	0/73	2/78		1.6 %	0.21 [0.01, 4.37]
Cindoruk 2007	0/62	1/62		1.5 %	0.33 [0.01, 8.03]
Duman 2005	0/204	1/185		1.4 %	0.30 [0.01, 7.38]
Gao 2010	9/171	20/84		10.7 %	0.22 [0.11, 0.46]
Hickson 2007	0/69	11/66		1.8 %	0.04 [0.00, 0.69]
Kotowska 2005	5/132	11/137		8.0 %	0.47 [0.17, 1.32]
Lonnermark 2010	4/118	0/121		1.7 %	9.23 [0.50, 169.51]
McFarland 1995	6/97	5/96		7.1 %	1.19 [0.38, 3.76]
Miller 2008a	4/95	7/94		6.8 %	0.57 [0.17, 1.87]
Miller 2008b	2/157	0/159		1.6 %	5.06 [0.25, 104.63]
Plummer 2004	2/69	5/69		4.6 %	0.40 [0.08, 1.99]
Pozzoni 2012	8/141	4/134		6.9 %	1.90 [0.59, 6.17]
Psaradellis 2010	2/233	5/239		4.5 %	0.41 [0.08, 2.09]
Rafiq 2007	5/45	22/55		9.3 %	0.28 [0.11, 0.67]
Ruszczynski 2008	3/120	7/120		5.9 %	0.43 [0.11, 1.62]
Safdar 2008	0/23	1/17		1.5 %	0.25 [0.01, 5.79]
Selinger 2011	0/62	0/62			Not estimable
Surawicz 1989	16/212	9/106		10.3 %	0.89 [0.41, 1.94]
Thomas 2001	3/152	3/150		4.7 %	0.99 [0.20, 4.81]



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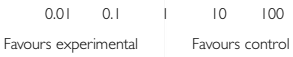
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Wenus 2008	2/34	1/29		2.5 %	1.71 [0.16, 17.87]
Total (95% CI)	**2443**	**2231**		**100.0 %**	**0.57 [0.38, 0.85]**

Total events: 76 (Experimental), 123 (Control)

Heterogeneity: $Tau^2 = 0.25$; $Chi^2 = 29.67$, df = 20 (P = 0.08); $I^2 = 33\%$

Test for overall effect: Z = 2.74 (P = 0.0061)

Test for subgroup differences: Not applicable



Analysis 1.7. Comparison 1 C. difficile associated diarrhea, Outcome 7 Incidence CDAD: Subgroup: Inpatient versus outpatient populations.

Review: Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children

Comparison: 1 C. difficile associated diarrhea

Outcome: 7 Incidence CDAD: Subgroup: Inpatient versus outpatient populations

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Inpatient					
Beausoleil 2007	1/44	7/45		2.9 %	0.15 [0.02, 1.14]
Can 2006	0/73	2/78		1.3 %	0.21 [0.01, 4.37]
Gao 2010	9/171	20/84		22.2 %	0.22 [0.11, 0.46]
Hickson 2007	0/57	9/56		1.5 %	0.05 [0.00, 0.87]
McFarland 1995	3/97	4/96		5.6 %	0.74 [0.17, 3.23]
Miller 2008a	4/95	7/94		8.5 %	0.57 [0.17, 1.87]
Miller 2008b	2/157	0/159		1.3 %	5.06 [0.25, 104.63]
Plummer 2004	2/69	5/69		4.7 %	0.40 [0.08, 1.99]
Pozzoni 2012	3/106	2/98		3.9 %	1.39 [0.24, 8.13]

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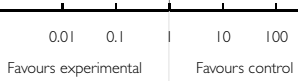
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Rafiq 2007	5/45	22/55		15.5 %	0.28 [0.11, 0.67]
Safdar 2008	0/23	1/17		1.2 %	0.25 [0.01, 5.79]
Selinger 2011	0/62	0/62			Not estimable
Surawicz 1989	3/116	5/64		6.2 %	0.33 [0.08, 1.34]
Thomas 2001	2/133	3/134		3.9 %	0.67 [0.11, 3.96]
Subtotal (95% CI)	**1248**	**1111**		**78.9 %**	**0.35 [0.24, 0.52]**
Total events: 34 (Experimental), 87 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 11.85$, df = 12 (P = 0.46); $I^2 = 0.0\%$					
Test for overall effect: Z = 5.25 (P < 0.00001)					
2 Outpatient					
Bravo 2008	0/41	0/45			Not estimable
Duman 2005	0/196	1/180		1.2 %	0.31 [0.01, 7.47]
Subtotal (95% CI)	**237**	**225**		**1.2 %**	**0.31 [0.01, 7.47]**
Total events: 0 (Experimental), 1 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.73 (P = 0.47)					
3 Mixed					
Arvola 1999	1/61	1/58		1.6 %	0.95 [0.06, 14.85]
Kotowska 2005	3/119	10/127		7.6 %	0.32 [0.09, 1.14]
Lonnermark 2010	1/80	0/83		1.2 %	3.11 [0.13, 75.26]
Psaradellis 2010	1/216	4/221		2.6 %	0.26 [0.03, 2.27]
Ruszczynski 2008	3/120	7/120		6.9 %	0.43 [0.11, 1.62]
Subtotal (95% CI)	**596**	**609**		**19.9 %**	**0.43 [0.20, 0.94]**
Total events: 9 (Experimental), 22 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 2.23$, df = 4 (P = 0.69); $I^2 = 0.0\%$					
Test for overall effect: Z = 2.11 (P = 0.035)					
Total (95% CI)	**2081**	**1945**		**100.0 %**	**0.36 [0.26, 0.52]**
Total events: 43 (Experimental), 110 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 14.31$, df = 18 (P = 0.71); $I^2 = 0.0\%$					
Test for overall effect: Z = 5.68 (P < 0.00001)					
Test for subgroup differences: $Chi^2 = 0.24$, df = 2 (P = 0.89), $I^2 = 0.0\%$					

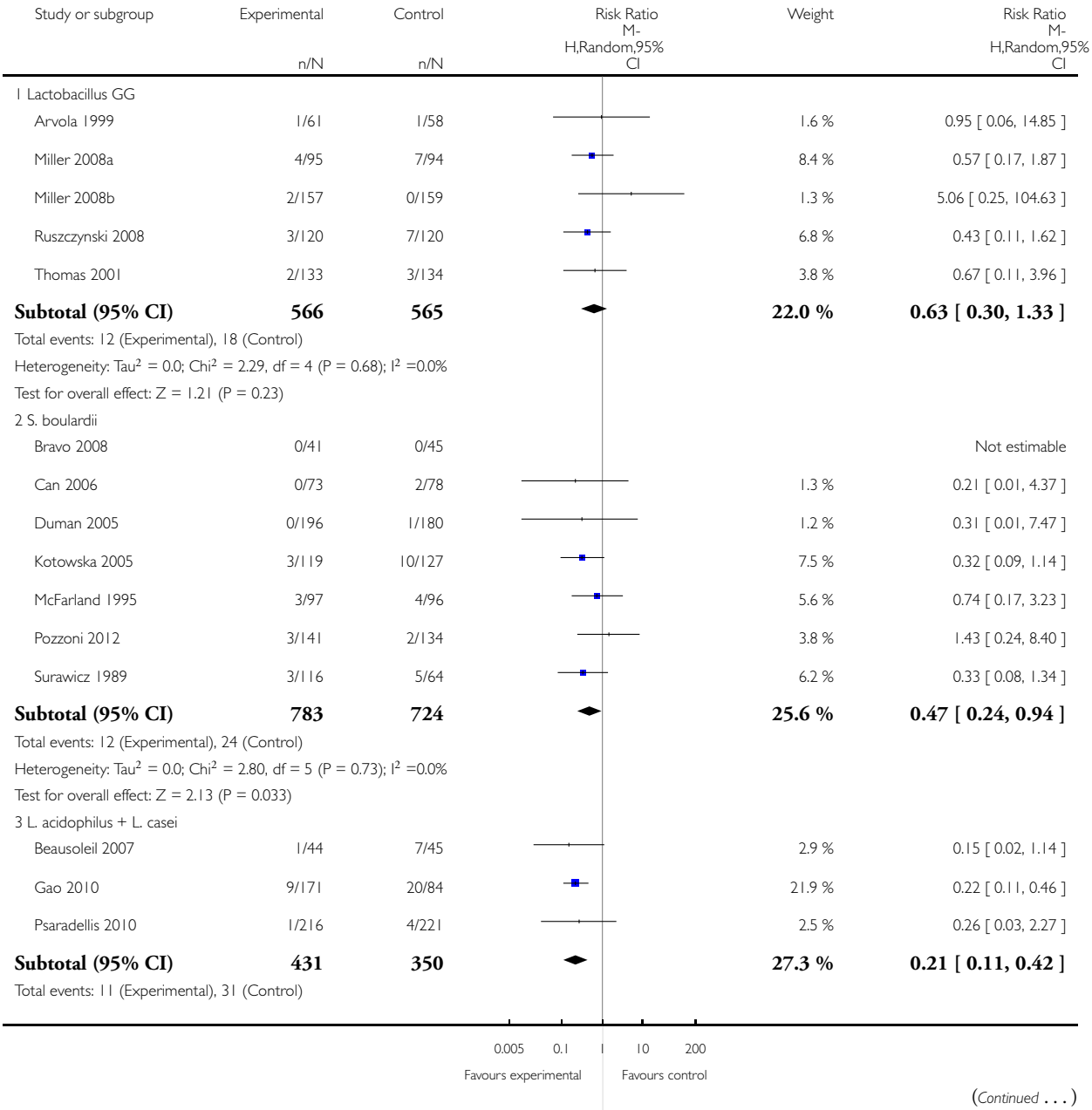


Analysis 1.8. Comparison 1 C. difficile associated diarrhea, Outcome 8 Incidence CDAD: Subgroup: Species: all.

Review: Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children

Comparison: 1 C. difficile associated diarrhea

Outcome: 8 Incidence CDAD: Subgroup: Species: all



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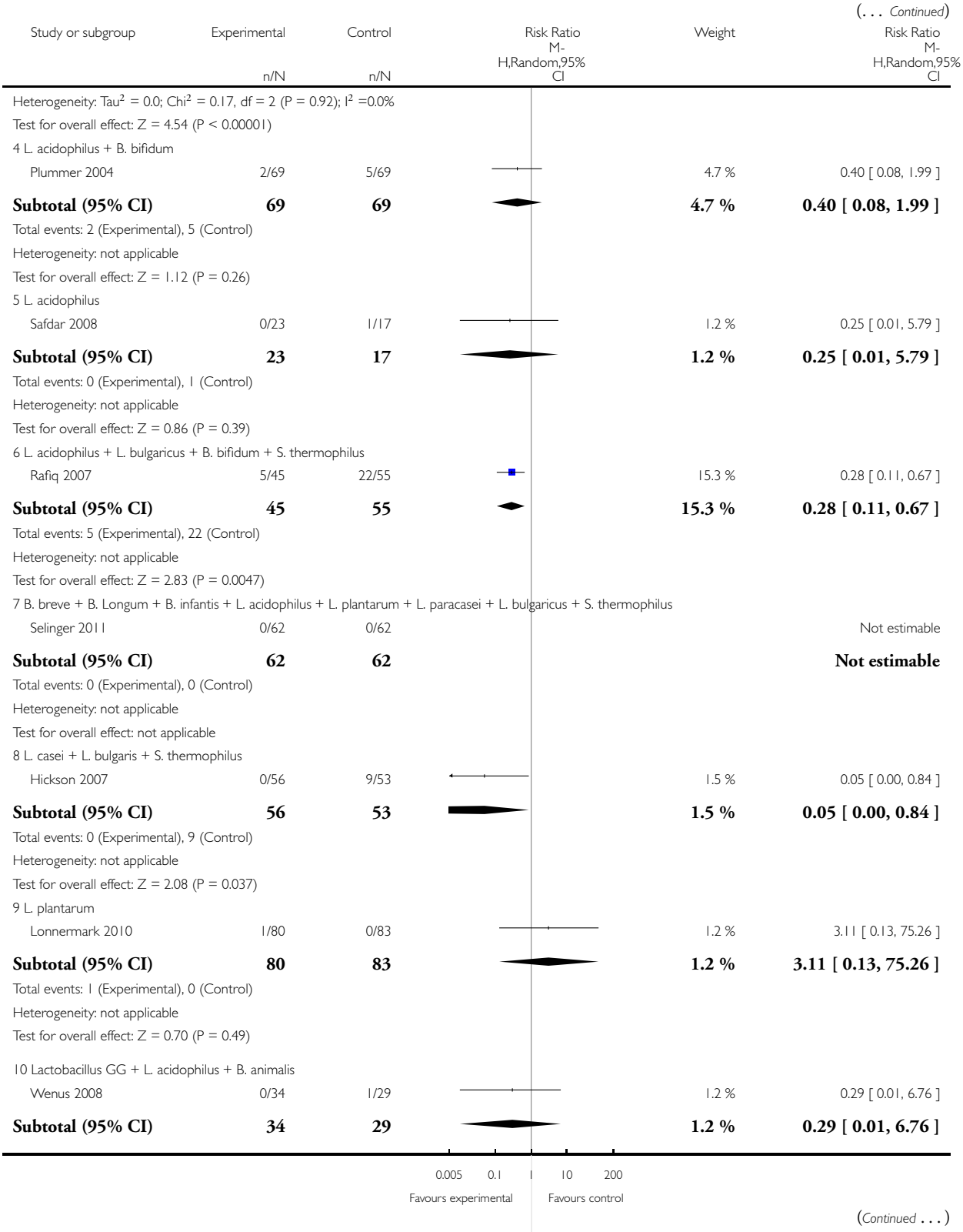

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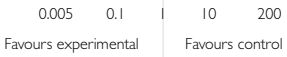
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Total events: 0 (Experimental), 1 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.78 (P = 0.44)					
Total (95% CI)	**2149**	**2007**	◆	**100.0 %**	**0.36 [0.26, 0.51]**
Total events: 43 (Experimental), 111 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 14.48, df = 19 (P = 0.75); I^2 =0.0%					
Test for overall effect: Z = 5.73 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 9.24, df = 8 (P = 0.32), I^2 =13%					



Analysis 1.9. Comparison 1 C. difficile associated diarrhea, Outcome 9 Incidence CDAD: Subgroup: Species: LGG versus SB.

Review: Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children

Comparison: 1 C. difficile associated diarrhea

Outcome: 9 Incidence CDAD: Subgroup: Species: LGG versus SB

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Lactobacillus GG					
Arvola 1999	1/61	1/58		3.4 %	0.95 [0.06, 14.85]
Miller 2008a	4/95	7/94		17.7 %	0.57 [0.17, 1.87]
Miller 2008b	2/157	0/159		2.8 %	5.06 [0.25, 104.63]
Ruszczynski 2008	3/120	7/120		14.3 %	0.43 [0.11, 1.62]
Thomas 2001	2/133	3/134		8.1 %	0.67 [0.11, 3.96]
Subtotal (95% CI)	**566**	**565**	◆	**46.2 %**	**0.63 [0.30, 1.33]**
Total events: 12 (Experimental), 18 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 2.29, df = 4 (P = 0.68); I^2 =0.0%					
Test for overall effect: Z = 1.21 (P = 0.23)					

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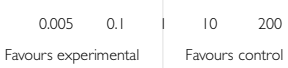
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
2 S. boulardii					
Bravo 2008	0/41	0/45			Not estimable
Can 2006	0/73	2/78		2.8 %	0.21 [0.01, 4.37]
Duman 2005	0/196	1/180		2.5 %	0.31 [0.01, 7.47]
Kotowska 2005	3/119	10/127		15.8 %	0.32 [0.09, 1.14]
McFarland 1995	3/97	4/96		11.7 %	0.74 [0.17, 3.23]
Pozzoni 2012	3/141	2/134		8.0 %	1.43 [0.24, 8.40]
Surawicz 1989	3/116	5/64		12.9 %	0.33 [0.08, 1.34]
Subtotal (95% CI)	**783**	**724**		**53.8 %**	**0.47 [0.24, 0.94]**
Total events: 12 (Experimental), 24 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 2.80, df = 5 (P = 0.73); I^2 =0.0%					
Test for overall effect: Z = 2.13 (P = 0.033)					
Total (95% CI)	**1349**	**1289**		**100.0 %**	**0.54 [0.33, 0.90]**
Total events: 24 (Experimental), 42 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 5.39, df = 10 (P = 0.86); I^2 =0.0%					
Test for overall effect: Z = 2.39 (P = 0.017)					
Test for subgroup differences: Chi^2 = 0.32, df = 1 (P = 0.57), I^2 =0.0%					

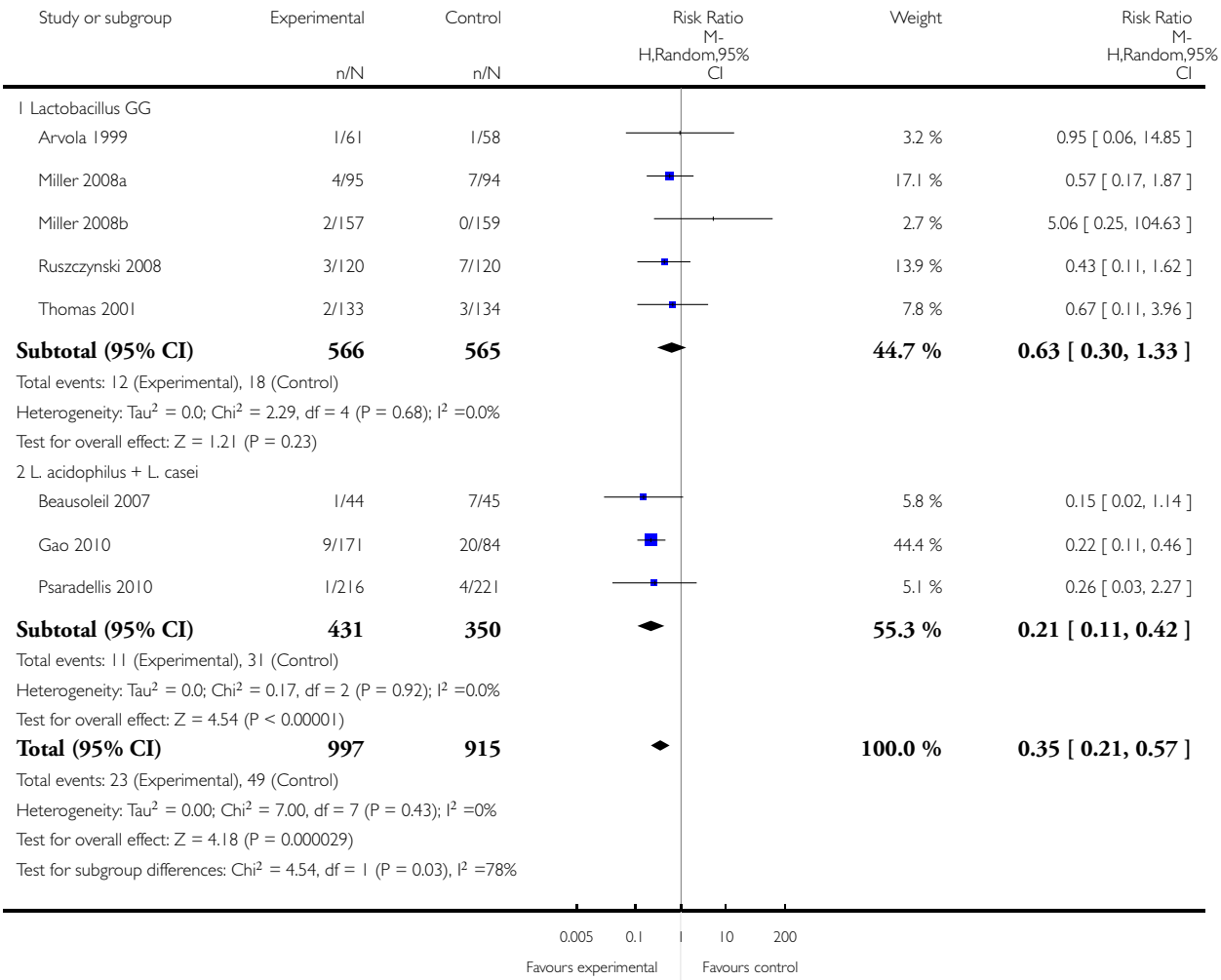


Analysis 1.10. Comparison 1 C. difficile associated diarrhea, Outcome 10 Incidence CDAD: Subgroup: Species: LGG versus LA + LC.

Review: Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children

Comparison: 1 C. difficile associated diarrhea

Outcome: 10 Incidence CDAD: Subgroup: Species: LGG versus LA + LC



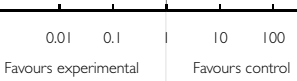
Analysis 1.11. Comparison 1 C. difficile associated diarrhea, Outcome 11 Incidence CDAD: Subgroup: Risk of Bias.

Review: Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children

Comparison: 1 C. difficile associated diarrhea

Outcome: 11 Incidence CDAD: Subgroup: Risk of Bias

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Low risk of bias					
Can 2006	0/73	2/78		1.3 %	0.21 [0.01, 4.37]
Gao 2010	9/171	20/84		21.9 %	0.22 [0.11, 0.46]
Hickson 2007	0/56	9/53		1.5 %	0.05 [0.00, 0.84]
Kotowska 2005	3/119	10/127		7.5 %	0.32 [0.09, 1.14]
Ruszczynski 2008	3/120	7/120		6.8 %	0.43 [0.11, 1.62]
Safdar 2008	0/23	1/17		1.2 %	0.25 [0.01, 5.79]
Thomas 2001	2/133	3/134		3.8 %	0.67 [0.11, 3.96]
Subtotal (95% CI)	**695**	**613**		**44.1 %**	**0.27 [0.16, 0.46]**
Total events: 17 (Experimental), 52 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 3.29$, df = 6 (P = 0.77); $I^2 = 0.0\%$					
Test for overall effect: Z = 4.86 (P < 0.00001)					
2 High or unclear risk of bias					
Arvola 1999	1/61	1/58		1.6 %	0.95 [0.06, 14.85]
Beausoleil 2007	1/44	7/45		2.9 %	0.15 [0.02, 1.14]
Bravo 2008	0/41	0/45			Not estimable
Cindoruk 2007	0/62	0/62			Not estimable
Duman 2005	0/196	1/180		1.2 %	0.31 [0.01, 7.47]
Lonnermark 2010	1/80	0/83		1.2 %	3.11 [0.13, 75.26]
McFarland 1995	3/97	4/96		5.6 %	0.74 [0.17, 3.23]
Miller 2008a	4/95	7/94		8.4 %	0.57 [0.17, 1.87]
Miller 2008b	2/157	0/159		1.3 %	5.06 [0.25, 104.63]
Plummer 2004	2/69	5/69		4.7 %	0.40 [0.08, 1.99]
Pozzoni 2012	3/141	2/134		3.8 %	1.43 [0.24, 8.40]
Psaradellis 2010	1/216	4/221		2.5 %	0.26 [0.03, 2.27]
Rafiq 2007	5/45	22/55		15.3 %	0.28 [0.11, 0.67]



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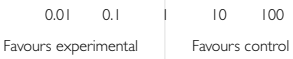
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Selinger 2011	0/62	0/62			Not estimable
Surawicz 1989	3/116	5/64		6.2 %	0.33 [0.08, 1.34]
Wenus 2008	0/34	1/29		1.2 %	0.29 [0.01, 6.76]
Subtotal (95% CI)	**1516**	**1456**		**55.9 %**	**0.45 [0.28, 0.72]**
Total events: 26 (Experimental), 59 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 9.25$, df = 12 (P = 0.68); $I^2 = 0.0\%$					
Test for overall effect: Z = 3.34 (P = 0.00083)					
Total (95% CI)	**2211**	**2069**		**100.0 %**	**0.36 [0.26, 0.51]**
Total events: 43 (Experimental), 111 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 14.48$, df = 19 (P = 0.75); $I^2 = 0.0\%$					
Test for overall effect: Z = 5.73 (P < 0.00001)					
Test for subgroup differences: $Chi^2 = 1.99$, df = 1 (P = 0.16), $I^2 = 50\%$					



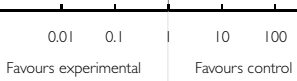
Analysis 1.12. Comparison 1 C. difficile associated diarrhea, Outcome 12 Incidence CDAD: Subgroup: Adult versus child.

Review: Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children

Comparison: 1 C. difficile associated diarrhea

Outcome: 12 Incidence CDAD: Subgroup: Adult versus child

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Adult studies					
Beausoleil 2007	1/44	7/45		2.9 %	0.15 [0.02, 1.14]
Bravo 2008	0/41	0/45			Not estimable
Can 2006	0/73	2/78		1.3 %	0.21 [0.01, 4.37]
Duman 2005	0/196	1/180		1.2 %	0.31 [0.01, 7.47]
Gao 2010	9/171	20/84		21.9 %	0.22 [0.11, 0.46]
Hickson 2007	0/56	9/53		1.5 %	0.05 [0.00, 0.84]
Lonnermark 2010	1/80	0/83		1.2 %	3.11 [0.13, 75.26]
McFarland 1995	3/97	4/96		5.6 %	0.74 [0.17, 3.23]
Miller 2008a	4/95	7/94		8.4 %	0.57 [0.17, 1.87]
Miller 2008b	2/157	0/159		1.3 %	5.06 [0.25, 104.63]
Plummer 2004	2/69	5/69		4.7 %	0.40 [0.08, 1.99]
Pozzoni 2012	3/141	2/134		3.8 %	1.43 [0.24, 8.40]
Psaradellis 2010	1/216	4/221		2.5 %	0.26 [0.03, 2.27]
Rafiq 2007	5/45	22/55		15.3 %	0.28 [0.11, 0.67]
Safdar 2008	0/23	1/17		1.2 %	0.25 [0.01, 5.79]
Selinger 2011	0/62	0/62			Not estimable
Surawicz 1989	3/116	5/64		6.2 %	0.33 [0.08, 1.34]
Thomas 2001	2/133	3/134		3.8 %	0.67 [0.11, 3.96]
Wenus 2008	0/34	1/29		1.2 %	0.29 [0.01, 6.76]
Subtotal (95% CI)	**1849**	**1702**		**84.1 %**	**0.36 [0.24, 0.52]**
Total events: 36 (Experimental), 93 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 13.90$, df = 16 (P = 0.61); $I^2 = 0.0\%$					
Test for overall effect: Z = 5.36 (P < 0.00001)					
2 Pediatric studies					
Arvola 1999	1/61	1/58		1.6 %	0.95 [0.06, 14.85]



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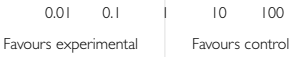
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Kotowska 2005	3/119	10/127		7.5 %	0.32 [0.09, 1.14]
Ruszczynski 2008	3/120	7/120		6.8 %	0.43 [0.11, 1.62]
Subtotal (95% CI)	**300**	**305**		**15.9 %**	**0.40 [0.17, 0.96]**
Total events: 7 (Experimental), 18 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.51$, df = 2 (P = 0.77); $I^2 = 0.0\%$					
Test for overall effect: Z = 2.04 (P = 0.041)					
Total (95% CI)	**2149**	**2007**		**100.0 %**	**0.36 [0.26, 0.51]**
Total events: 43 (Experimental), 111 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 14.48$, df = 19 (P = 0.75); $I^2 = 0.0\%$					
Test for overall effect: Z = 5.73 (P < 0.00001)					
Test for subgroup differences: $Chi^2 = 0.07$, df = 1 (P = 0.79), $I^2 = 0.0\%$					



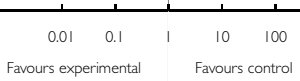
Analysis 2.1. Comparison 2 Adverse events, Outcome 1 Adverse Events: complete case.

Review: Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children

Comparison: 2 Adverse events

Outcome: 1 Adverse Events: complete case

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Arvola 1999	0/61	0/58			Not estimable
Beausoleil 2007	21/44	20/45		8.3 %	1.07 [0.68, 1.68]
Bravo 2008	3/41	4/45		1.3 %	0.82 [0.20, 3.46]
Cindoruk 2007	41/62	62/62		17.1 %	0.66 [0.56, 0.79]
Duman 2005	3/196	4/180		1.2 %	0.69 [0.16, 3.04]
Gao 2010	1/171	2/84		0.5 %	0.25 [0.02, 2.67]
Hickson 2007	0/57	0/56			Not estimable
Imase 2008	1/12	3/7		0.6 %	0.19 [0.02, 1.53]
Klarin 2008	0/22	0/22			Not estimable
Koning 2008	15/19	17/19		13.3 %	0.88 [0.67, 1.17]
Kotowska 2005	0/119	0/127			Not estimable
Lonnermark 2010	3/80	3/83		1.1 %	1.04 [0.22, 4.99]
McFarland 1995	0/93	12/92		0.3 %	0.04 [0.00, 0.66]
Miller 2008a	2/95	4/94		0.9 %	0.49 [0.09, 2.64]
Miller 2008b	4/157	0/159		0.3 %	9.11 [0.49, 167.88]
Nord 1997	9/11	10/12		10.2 %	0.98 [0.67, 1.43]
Pozzoni 2012	41/106	35/98		10.7 %	1.08 [0.76, 1.55]
Psaradellis 2010	90/216	103/221		15.9 %	0.89 [0.72, 1.10]
Ruszczynski 2008	0/120	0/120			Not estimable
Safdar 2008	2/23	5/17		1.1 %	0.30 [0.06, 1.35]
Selinger 2011	3/62	3/62		1.1 %	1.00 [0.21, 4.76]
Shimbo 2005	5/18	14/17		3.8 %	0.34 [0.16, 0.73]
Siitonen 1990	2/8	3/8		1.2 %	0.67 [0.15, 2.98]
Sullivan 2004	0/18	0/18			Not estimable
Surawicz 1989	0/116	0/64			Not estimable



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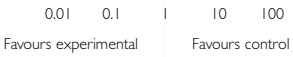
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Thomas 2001	37/133	52/134		11.1 %	0.72 [0.51, 1.01]
Total (95% CI)	**2060**	**1904**		**100.0 %**	**0.80 [0.68, 0.95]**

Total events: 283 (Experimental), 356 (Control)

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 28.47$, df = 18 (P = 0.06); $I^2 = 37\%$

Test for overall effect: Z = 2.63 (P = 0.0087)

Test for subgroup differences: Not applicable



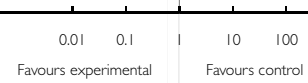
Analysis 2.2. Comparison 2 Adverse events, Outcome 2 Adverse Events: Subgroup: Risk of Bias.

Review: Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children

Comparison: 2 Adverse events

Outcome: 2 Adverse Events: Subgroup: Risk of Bias

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Low Risk of Bias					
Beausoleil 2007	21/44	20/45		8.4 %	1.07 [0.68, 1.68]
Bravo 2008	3/41	4/45		1.3 %	0.82 [0.20, 3.46]
Cindoruk 2007	41/62	62/62		17.2 %	0.66 [0.56, 0.79]
Gao 2010	1/171	2/84		0.5 %	0.25 [0.02, 2.67]
Koning 2008	15/19	17/19		13.4 %	0.88 [0.67, 1.17]
Kotowska 2005	0/119	0/127			Not estimable
Nord 1997	9/11	10/12		10.3 %	0.98 [0.67, 1.43]
Pozzoni 2012	41/141	35/134		10.1 %	1.11 [0.76, 1.63]
Psaradellis 2010	90/216	103/221		15.9 %	0.89 [0.72, 1.10]
Ruszczynski 2008	0/120	0/120			Not estimable



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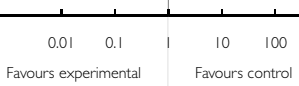
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Safdar 2008	2/23	5/17		1.2 %	0.30 [0.06, 1.35]
Thomas 2001	37/133	52/134		11.2 %	0.72 [0.51, 1.01]
Subtotal (95% CI)	**1100**	**1020**		**89.4 %**	**0.84 [0.72, 0.98]**
Total events: 260 (Experimental), 310 (Control)					
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 14.58$, df = 9 (P = 0.10); $I^2 = 38\%$					
Test for overall effect: Z = 2.24 (P = 0.025)					
2 High/Unclear risk of bias					
Arvola 1999	0/61	0/58			Not estimable
Duman 2005	3/196	4/180		1.2 %	0.69 [0.16, 3.04]
Hickson 2007	0/56	0/53			Not estimable
Imase 2008	1/12	3/7		0.6 %	0.19 [0.02, 1.53]
Klarin 2008	0/22	0/22			Not estimable
Lonnermark 2010	3/80	3/83		1.1 %	1.04 [0.22, 4.99]
McFarland 1995	0/93	12/92		0.3 %	0.04 [0.00, 0.66]
Miller 2008a	2/95	4/94		1.0 %	0.49 [0.09, 2.64]
Miller 2008b	4/157	0/159		0.3 %	9.11 [0.49, 167.88]
Selinger 2011	3/62	3/62		1.1 %	1.00 [0.21, 4.76]
Shimbo 2005	5/18	14/17		3.8 %	0.34 [0.16, 0.73]
Siitonen 1990	2/8	3/8		1.2 %	0.67 [0.15, 2.98]
Sullivan 2004	0/18	0/18			Not estimable
Surawicz 1989	0/116	0/64			Not estimable
Subtotal (95% CI)	**994**	**917**		**10.6 %**	**0.54 [0.29, 0.99]**
Total events: 23 (Experimental), 46 (Control)					
Heterogeneity: $Tau^2 = 0.21$; $Chi^2 = 10.65$, df = 8 (P = 0.22); $I^2 = 25\%$					
Test for overall effect: Z = 2.00 (P = 0.045)					
Total (95% CI)	**2094**	**1937**		**100.0 %**	**0.80 [0.68, 0.95]**
Total events: 283 (Experimental), 356 (Control)					
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 28.53$, df = 18 (P = 0.05); $I^2 = 37\%$					
Test for overall effect: Z = 2.60 (P = 0.0093)					
Test for subgroup differences: $Chi^2 = 1.97$, df = 1 (P = 0.16), $I^2 = 49\%$					



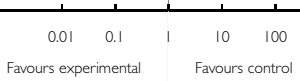
Analysis 2.3. Comparison 2 Adverse events, Outcome 3 AE Sensitivity 1.5:1.

Review: Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children

Comparison: 2 Adverse events

Outcome: 3 AE Sensitivity 1.5:1

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Arvola 1999	0/89	0/78			Not estimable
Beausoleil 2007	21/44	20/45		8.4 %	1.07 [0.68, 1.68]
Bravo 2008	3/41	4/45		1.4 %	0.82 [0.20, 3.46]
Cindoruk 2007	41/62	62/62		15.1 %	0.66 [0.56, 0.79]
Duman 2005	3/204	4/185		1.4 %	0.68 [0.15, 3.00]
Gao 2010	1/171	2/84		0.5 %	0.25 [0.02, 2.67]
Hickson 2007	0/69	0/66			Not estimable
Imase 2008	1/12	3/7		0.7 %	0.19 [0.02, 1.53]
Klarin 2008	0/24	0/24			Not estimable
Koning 2008	16/20	19/21		13.0 %	0.88 [0.68, 1.15]
Kotowska 2005	0/132	0/137			Not estimable
Lonnermark 2010	5/118	4/121		1.7 %	1.28 [0.35, 4.66]
McFarland 1995	0/97	14/96		0.4 %	0.03 [0.00, 0.56]
Miller 2008a	2/95	4/94		1.1 %	0.49 [0.09, 2.64]
Miller 2008b	4/157	0/159		0.4 %	9.11 [0.49, 167.88]
Nord 1997	9/11	10/12		10.0 %	0.98 [0.67, 1.43]
Pozzoni 2012	61/141	48/134		12.0 %	1.21 [0.90, 1.62]
Psaradellis 2010	101/233	111/239		14.5 %	0.93 [0.76, 1.14]
Ruszczynski 2008	0/120	0/120			Not estimable
Safdar 2008	2/23	5/17		1.3 %	0.30 [0.06, 1.35]
Selinger 2011	3/62	3/62		1.2 %	1.00 [0.21, 4.76]
Shimbo 2005	5/18	14/17		4.1 %	0.34 [0.16, 0.73]
Siitonen 1990	2/8	3/8		1.3 %	0.67 [0.15, 2.98]
Sullivan 2004	0/32	0/32			Not estimable
Surawicz 1989	0/212	0/106			Not estimable



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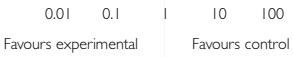
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Thomas 2001	45/152	58/150		11.4 %	0.77 [0.56, 1.05]
Total (95% CI)	**2347**	**2121**		**100.0 %**	**0.82 [0.69, 0.99]**

Total events: 325 (Experimental), 388 (Control)

Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 34.42$, df = 18 (P = 0.01); $I^2 = 48\%$

Test for overall effect: Z = 2.11 (P = 0.035)

Test for subgroup differences: Not applicable



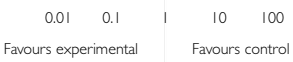
Analysis 2.4. Comparison 2 Adverse events, Outcome 4 AE Sensitivity 2:1.

Review: Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children

Comparison: 2 Adverse events

Outcome: 4 AE Sensitivity 2:1

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Arvola 1999	0/89	0/78			Not estimable
Beausoleil 2007	21/44	20/45		8.5 %	1.07 [0.68, 1.68]
Bravo 2008	3/41	4/45		1.6 %	0.82 [0.20, 3.46]
Cindoruk 2007	41/62	62/62		14.0 %	0.66 [0.56, 0.79]
Duman 2005	4/204	4/185		1.8 %	0.91 [0.23, 3.57]
Gao 2010	1/171	2/84		0.6 %	0.25 [0.02, 2.67]
Hickson 2007	0/69	0/66			Not estimable
Imase 2008	1/12	3/7		0.8 %	0.19 [0.02, 1.53]
Klarin 2008	0/24	0/24			Not estimable
Koning 2008	17/20	19/21		13.0 %	0.94 [0.75, 1.18]
Kotowska 2005	0/132	0/137			Not estimable



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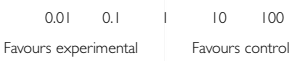
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Lonnermark 2010	6/118	4/121		2.1 %	1.54 [0.45, 5.31]
McFarland 1995	0/97	14/96		0.5 %	0.03 [0.00, 0.56]
Miller 2008a	2/95	4/94		1.2 %	0.49 [0.09, 2.64]
Miller 2008b	4/157	0/159		0.4 %	9.11 [0.49, 167.88]
Nord 1997	9/11	10/12		9.9 %	0.98 [0.67, 1.43]
Pozzoni 2012	68/141	48/134		11.8 %	1.35 [1.01, 1.79]
Psaradellis 2010	104/233	111/239		13.6 %	0.96 [0.79, 1.17]
Ruszczynski 2008	0/120	0/120			Not estimable
Safdar 2008	2/23	5/17		1.5 %	0.30 [0.06, 1.35]
Selinger 2011	3/62	3/62		1.4 %	1.00 [0.21, 4.76]
Shimbo 2005	5/18	14/17		4.4 %	0.34 [0.16, 0.73]
Siitonen 1990	2/8	3/8		1.5 %	0.67 [0.15, 2.98]
Sullivan 2004	0/32	0/32			Not estimable
Surawicz 1989	0/212	0/106			Not estimable
Thomas 2001	48/152	58/150		11.3 %	0.82 [0.60, 1.11]
Total (95% CI)	**2347**	**2121**		**100.0 %**	**0.85 [0.70, 1.03]**

Total events: 341 (Experimental), 388 (Control)

Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 40.45$, df = 18 (P = 0.002); $I^2 = 56\%$

Test for overall effect: Z = 1.62 (P = 0.11)

Test for subgroup differences: Not applicable



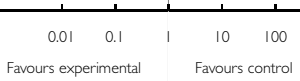
Analysis 2.5. Comparison 2 Adverse events, Outcome 5 AE Sensitivity 3:1.

Review: Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children

Comparison: 2 Adverse events

Outcome: 5 AE Sensitivity 3:1

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Arvola 1999	0/89	0/78			Not estimable
Beausoleil 2007	21/44	20/45		8.8 %	1.07 [0.68, 1.68]
Bravo 2008	3/41	4/45		2.0 %	0.82 [0.20, 3.46]
Cindoruk 2007	41/62	62/62		12.6 %	0.66 [0.56, 0.79]
Duman 2005	4/204	4/185		2.2 %	0.91 [0.23, 3.57]
Gao 2010	1/171	2/84		0.8 %	0.25 [0.02, 2.67]
Hickson 2007	0/69	0/66			Not estimable
Imase 2008	1/12	3/7		1.1 %	0.19 [0.02, 1.53]
Klarin 2008	0/24	0/24			Not estimable
Koning 2008	17/20	19/21		11.9 %	0.94 [0.75, 1.18]
Kotowska 2005	0/132	0/137			Not estimable
Lonnermark 2010	7/118	4/121		2.7 %	1.79 [0.54, 5.97]
McFarland 1995	0/97	14/96		0.6 %	0.03 [0.00, 0.56]
Miller 2008a	2/95	4/94		1.6 %	0.49 [0.09, 2.64]
Miller 2008b	4/157	0/159		0.6 %	9.11 [0.49, 167.88]
Nord 1997	9/11	10/12		9.8 %	0.98 [0.67, 1.43]
Pozzoni 2012	82/141	48/134		11.4 %	1.62 [1.24, 2.12]
Psaradellis 2010	111/233	111/239		12.4 %	1.03 [0.85, 1.24]
Ruszczynski 2008	0/120	0/120			Not estimable
Safdar 2008	2/23	5/17		1.9 %	0.30 [0.06, 1.35]
Selinger 2011	3/62	3/62		1.8 %	1.00 [0.21, 4.76]
Shimbo 2005	5/18	14/17		5.1 %	0.34 [0.16, 0.73]
Siitonen 1990	2/8	3/8		1.9 %	0.67 [0.15, 2.98]
Sullivan 2004	0/32	0/32			Not estimable
Surawicz 1989	0/212	0/106			Not estimable



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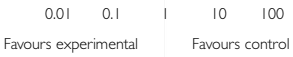
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Thomas 2001	53/152	58/150		11.0 %	0.90 [0.67, 1.21]
Total (95% CI)	**2347**	**2121**		**100.0 %**	**0.88 [0.70, 1.10]**

Total events: 368 (Experimental), 388 (Control)

Heterogeneity: $Tau^2 = 0.09$; $Chi^2 = 53.96$, df = 18 (P = 0.00002); $I^2 = 67\%$

Test for overall effect: Z = 1.16 (P = 0.25)

Test for subgroup differences: Not applicable



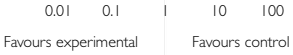
Analysis 2.6. Comparison 2 Adverse events, Outcome 6 AE Sensitivity 5:1.

Review: Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children

Comparison: 2 Adverse events

Outcome: 6 AE Sensitivity 5:1

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Arvola 1999	0/89	0/78			Not estimable
Beausoleil 2007	21/44	20/45		8.7 %	1.07 [0.68, 1.68]
Bravo 2008	3/41	4/45		2.6 %	0.82 [0.20, 3.46]
Cindoruk 2007	41/62	62/62		11.0 %	0.66 [0.56, 0.79]
Duman 2005	4/204	4/185		2.8 %	0.91 [0.23, 3.57]
Gao 2010	1/171	2/84		1.1 %	0.25 [0.02, 2.67]
Hickson 2007	0/69	0/66			Not estimable
Imase 2008	1/12	3/7		1.4 %	0.19 [0.02, 1.53]
Klarin 2008	0/24	0/24			Not estimable
Koning 2008	19/20	19/21		11.1 %	1.05 [0.88, 1.25]
Kotowska 2005	0/132	0/137			Not estimable



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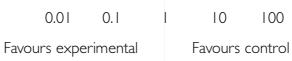
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Lonnermark 2010	10/118	4/121		3.7 %	2.56 [0.83, 7.95]
McFarland 1995	0/97	14/96		0.8 %	0.03 [0.00, 0.56]
Miller 2008a	2/95	4/94		2.0 %	0.49 [0.09, 2.64]
Miller 2008b	4/157	0/159		0.8 %	9.11 [0.49, 167.88]
Nord 1997	9/11	10/12		9.4 %	0.98 [0.67, 1.43]
Pozzoni 2012	109/141	48/134		10.6 %	2.16 [1.69, 2.75]
Psaradellis 2010	125/233	111/239		11.0 %	1.16 [0.96, 1.38]
Ruszczynski 2008	0/120	0/120			Not estimable
Safdar 2008	2/23	5/17		2.4 %	0.30 [0.06, 1.35]
Selinger 2011	3/62	3/62		2.3 %	1.00 [0.21, 4.76]
Shimbo 2005	5/18	14/17		5.7 %	0.34 [0.16, 0.73]
Siitonen 1990	2/8	3/8		2.4 %	0.67 [0.15, 2.98]
Sullivan 2004	0/32	0/32			Not estimable
Surawicz 1989	0/212	0/106			Not estimable
Thomas 2001	63/152	58/150		10.3 %	1.07 [0.81, 1.41]
Total (95% CI)	**2347**	**2121**		**100.0 %**	**0.93 [0.72, 1.21]**

Total events: 424 (Experimental), 388 (Control)

Heterogeneity: $Tau^2 = 0.15$; $Chi^2 = 87.55$, df = 18 ($P<0.00001$); $I^2 = 79\%$

Test for overall effect: Z = 0.51 (P = 0.61)

Test for subgroup differences: Not applicable

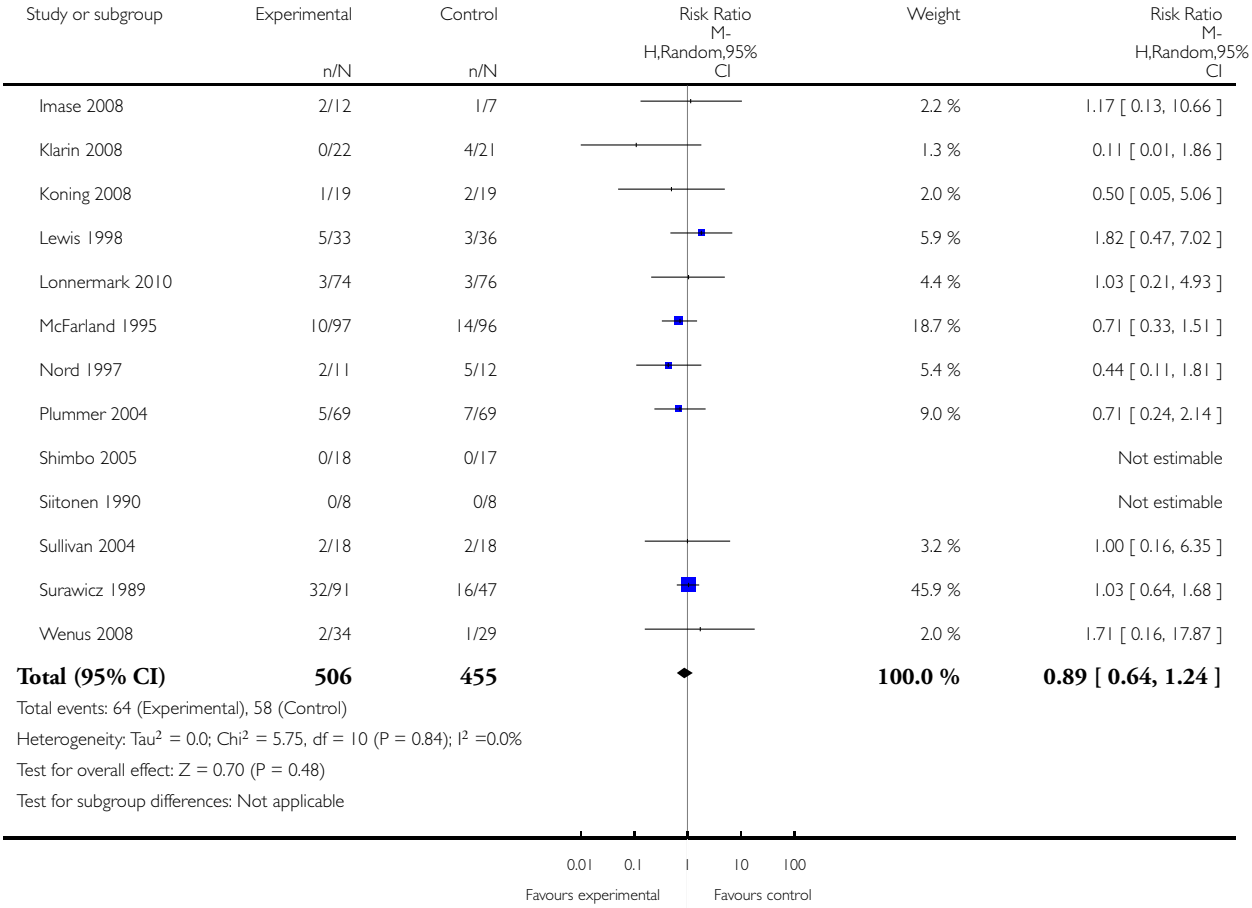


Analysis 3.1. Comparison 3 Incidence of Clostridium difficile infection, Outcome 1 Incidence of infection: complete case.

Review: Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children

Comparison: 3 Incidence of Clostridium difficile infection

Outcome: 1 Incidence of infection: complete case

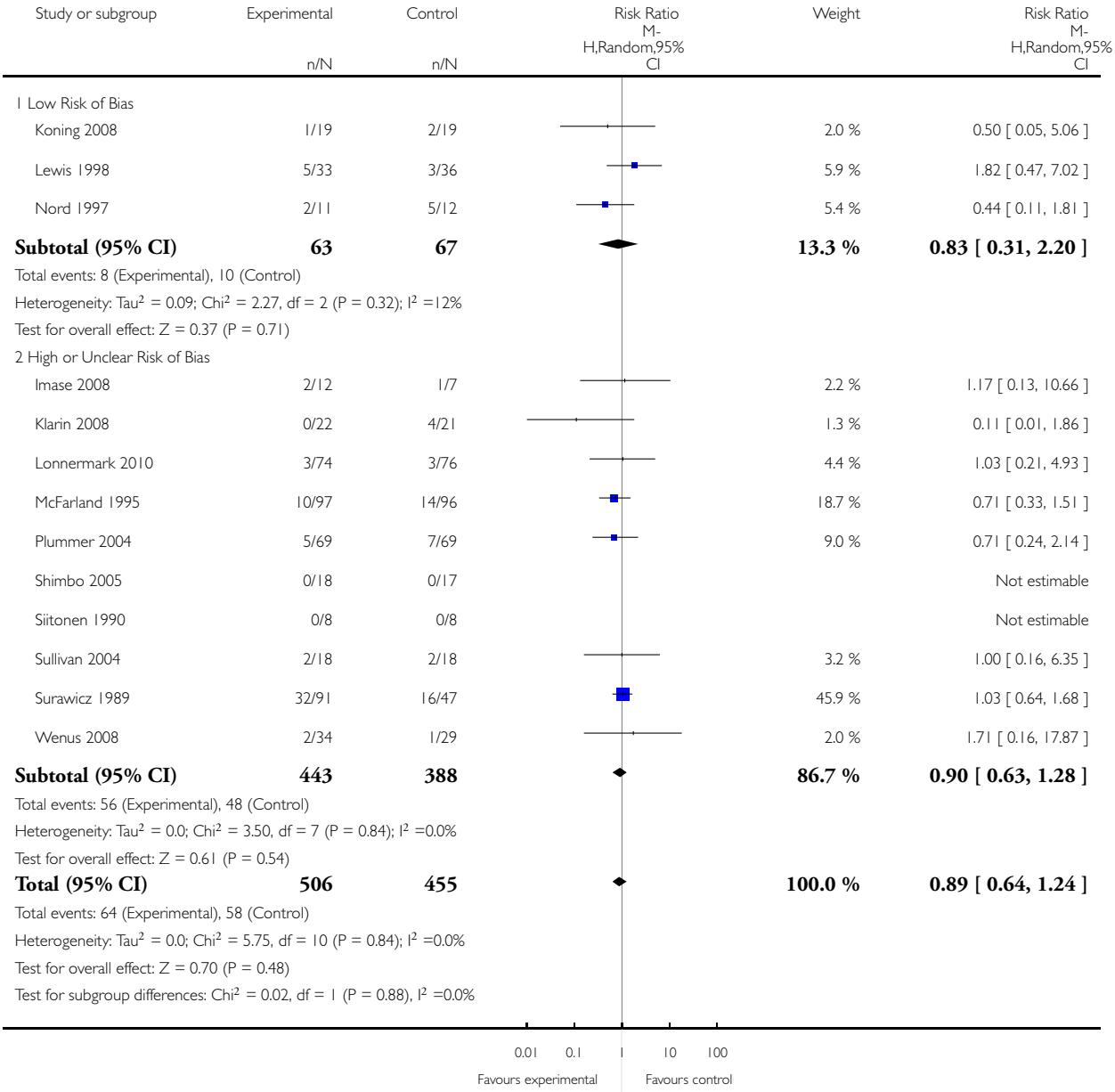


Analysis 3.2. Comparison 3 Incidence of Clostridium difficile infection, Outcome 2 Incidence of infection: Subgroup: Risk of Bias.

Review: Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children

Comparison: 3 Incidence of Clostridium difficile infection

Outcome: 2 Incidence of infection: Subgroup: Risk of Bias



Analysis 4.1. Comparison 4 Length of hospital stay, Outcome 1 Length of Hospital Stay: complete case.

Review: Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children

Comparison: 4 Length of hospital stay

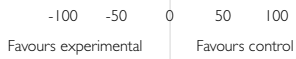
Outcome: 1 Length of Hospital Stay: complete case

Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Beausoleil 2007	44	12.2 (9.6)	45	16.4 (16.5)		22.6 %	-4.20 [-9.79, 1.39]
Selinger 2011	31	11.13 (13.83)	35	10.27 (10.09)		20.6 %	0.86 [-5.05, 6.77]
Thomas 2001	133	5.1 (11.72)	134	4.3 (13.3)		56.7 %	0.80 [-2.21, 3.81]
Total (95% CI)	**208**		**214**			**100.0 %**	**-0.32 [-3.21, 2.57]**

Heterogeneity: $Tau^2 = 1.49$; $Chi^2 = 2.51$, df = 2 (P = 0.29); $I^2 = 20\%$

Test for overall effect: Z = 0.22 (P = 0.83)

Test for subgroup differences: Not applicable



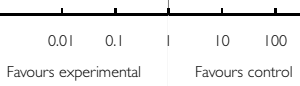
Analysis 5.1. Comparison 5 Antibiotic associated diarrhea, Outcome 1 Incidence AAD: complete case.

Review: Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children

Comparison: 5 Antibiotic associated diarrhea

Outcome: 1 Incidence AAD: complete case

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Arvola 1999	3/61	9/58		1.9 %	0.32 [0.09, 1.11]
Beausoleil 2007	7/44	16/45		4.1 %	0.45 [0.20, 0.98]
Bravo 2008	4/41	5/45		2.0 %	0.88 [0.25, 3.05]
Can 2006	1/73	7/78		0.8 %	0.15 [0.02, 1.21]
Cindoruk 2007	9/62	19/62		4.7 %	0.47 [0.23, 0.96]
Duman 2005	14/204	28/185		5.6 %	0.45 [0.25, 0.83]
Gao 2010	37/171	37/84		8.9 %	0.49 [0.34, 0.71]
Hickson 2007	7/57	19/56		4.1 %	0.36 [0.17, 0.79]
Imase 2008	1/12	3/7		0.8 %	0.19 [0.02, 1.53]
Koning 2008	9/19	15/19		6.6 %	0.60 [0.35, 1.02]
Kotowska 2005	9/119	29/127		4.7 %	0.33 [0.16, 0.67]
Lewis 1998	7/33	5/36		2.6 %	1.53 [0.54, 4.35]
Lonnermark 2010	6/80	5/83		2.3 %	1.25 [0.40, 3.92]
McFarland 1995	7/97	14/96		3.6 %	0.49 [0.21, 1.17]
Miller 2008b	8/157	4/159		2.2 %	2.03 [0.62, 6.59]
Plummer 2004	20/69	24/69		7.1 %	0.83 [0.51, 1.36]
Pozzoni 2012	16/106	13/98		4.9 %	1.14 [0.58, 2.24]
Psaradellis 2010	47/216	65/221		9.7 %	0.74 [0.53, 1.02]
Ruszczynski 2008	9/120	20/120		4.4 %	0.45 [0.21, 0.95]
Safdar 2008	4/23	6/16		2.5 %	0.46 [0.16, 1.38]
Selinger 2011	2/62	5/62		1.3 %	0.40 [0.08, 1.98]
Shimbo 2005	1/18	2/17		0.6 %	0.47 [0.05, 4.74]
Surawicz 1989	11/116	14/64		4.5 %	0.43 [0.21, 0.90]
Thomas 2001	39/133	40/134		8.9 %	0.98 [0.68, 1.42]
Wenus 2008	2/34	8/29		1.5 %	0.21 [0.05, 0.93]



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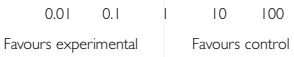
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Total (95% CI)	**2127**	**1970**	♦	**100.0 %**	**0.60 [0.49, 0.72]**
Total events: 280 (Experimental), 412 (Control)					
Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 37.30$, df = 24 (P = 0.04); $I^2 = 36\%$					
Test for overall effect: Z = 5.34 (P < 0.00001)					
Test for subgroup differences: Not applicable					



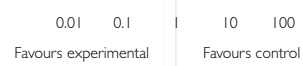
Analysis 5.2. Comparison 5 Antibiotic associated diarrhea, Outcome 2 Incidence AAD: Subgroup: Risk of Bias.

Review: Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children

Comparison: 5 Antibiotic associated diarrhea

Outcome: 2 Incidence AAD: Subgroup: Risk of Bias

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Low risk of bias					
Beausoleil 2007	7/44	16/45		4.1 %	0.45 [0.20, 0.98]
Bravo 2008	4/41	5/45		2.0 %	0.88 [0.25, 3.05]
Can 2006	1/73	7/78		0.8 %	0.15 [0.02, 1.21]
Cindoruk 2007	9/62	19/62		4.7 %	0.47 [0.23, 0.96]
Gao 2010	37/171	37/84		8.9 %	0.49 [0.34, 0.71]
Hickson 2007	7/57	19/56		4.1 %	0.36 [0.17, 0.79]
Koning 2008	9/19	15/19		6.6 %	0.60 [0.35, 1.02]
Kotowska 2005	9/119	29/127		4.7 %	0.33 [0.16, 0.67]
Lewis 1998	7/33	5/36		2.6 %	1.53 [0.54, 4.35]
Psaradellis 2010	47/216	65/221		9.7 %	0.74 [0.53, 1.02]



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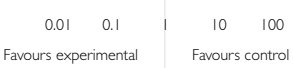
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Ruszczynski 2008	9/120	20/120		4.4 %	0.45 [0.21, 0.95]
Safdar 2008	4/23	6/16		2.5 %	0.46 [0.16, 1.38]
Thomas 2001	39/133	40/134		8.9 %	0.98 [0.68, 1.42]
Subtotal (95% CI)	**1111**	**1043**		**63.7 %**	**0.58 [0.46, 0.73]**
Total events: 189 (Experimental), 283 (Control)					
Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 20.66$, df = 12 (P = 0.06); $I^2 = 42\%$					
Test for overall effect: Z = 4.53 (P < 0.00001)					
2 High or Unclear risk of bias					
Arvola 1999	3/61	9/58		1.9 %	0.32 [0.09, 1.11]
Duman 2005	14/204	28/185		5.6 %	0.45 [0.25, 0.83]
Imase 2008	1/12	3/7		0.8 %	0.19 [0.02, 1.53]
Lonnermark 2010	6/80	5/83		2.3 %	1.25 [0.40, 3.92]
McFarland 1995	7/97	14/96		3.6 %	0.49 [0.21, 1.17]
Miller 2008b	8/157	4/159		2.2 %	2.03 [0.62, 6.59]
Plummer 2004	20/69	24/69		7.1 %	0.83 [0.51, 1.36]
Pozzoni 2012	16/106	13/98		4.9 %	1.14 [0.58, 2.24]
Selinger 2011	2/62	5/62		1.3 %	0.40 [0.08, 1.98]
Shimbo 2005	1/18	2/17		0.6 %	0.47 [0.05, 4.74]
Surawicz 1989	11/116	14/64		4.5 %	0.43 [0.21, 0.90]
Wenus 2008	2/34	8/29		1.5 %	0.21 [0.05, 0.93]
Subtotal (95% CI)	**1016**	**927**		**36.3 %**	**0.62 [0.44, 0.88]**
Total events: 91 (Experimental), 129 (Control)					
Heterogeneity: $Tau^2 = 0.11$; $Chi^2 = 16.57$, df = 11 (P = 0.12); $I^2 = 34\%$					
Test for overall effect: Z = 2.72 (P = 0.0065)					
Total (95% CI)	**2127**	**1970**		**100.0 %**	**0.60 [0.49, 0.72]**
Total events: 280 (Experimental), 412 (Control)					
Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 37.30$, df = 24 (P = 0.04); $I^2 = 36\%$					
Test for overall effect: Z = 5.34 (P < 0.00001)					
Test for subgroup differences: $Chi^2 = 0.11$, df = 1 (P = 0.74), $I^2 = 0.0\%$					



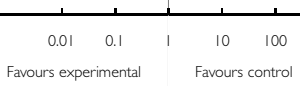
Analysis 5.3. Comparison 5 Antibiotic associated diarrhea, Outcome 3 Incidence AAD: sensitivity (1.5:1).

Review: Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children

Comparison: 5 Antibiotic associated diarrhea

Outcome: 3 Incidence AAD: sensitivity (1.5:1)

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Arvola 1999	12/89	13/78		3.9 %	0.81 [0.39, 1.67]
Beausoleil 2007	7/44	16/45		3.5 %	0.45 [0.20, 0.98]
Bravo 2008	4/41	5/45		1.7 %	0.88 [0.25, 3.05]
Can 2006	1/73	7/78		0.7 %	0.15 [0.02, 1.21]
Cindoruk 2007	9/62	19/62		4.0 %	0.47 [0.23, 0.96]
Duman 2005	14/204	28/185		4.9 %	0.45 [0.25, 0.83]
Gao 2010	37/171	37/84		7.9 %	0.49 [0.34, 0.71]
Hickson 2007	11/69	21/66		4.6 %	0.50 [0.26, 0.96]
Imase 2008	1/12	3/7		0.7 %	0.19 [0.02, 1.53]
Koning 2008	9/20	15/21		5.5 %	0.63 [0.36, 1.10]
Kotowska 2005	13/132	31/137		5.0 %	0.44 [0.24, 0.79]
Lewis 1998	7/35	5/38		2.2 %	1.52 [0.53, 4.35]
Lonnermark 2010	18/118	13/121		4.4 %	1.42 [0.73, 2.77]
McFarland 1995	7/97	14/96		3.1 %	0.49 [0.21, 1.17]
Miller 2008b	8/157	4/159		1.8 %	2.03 [0.62, 6.59]
Plummer 2004	20/69	24/69		6.2 %	0.83 [0.51, 1.36]
Pozzoni 2012	27/141	21/134		5.9 %	1.22 [0.73, 2.05]
Psaradellis 2010	52/233	69/239		8.9 %	0.77 [0.57, 1.06]
Ruszczynski 2008	9/120	20/120		3.8 %	0.45 [0.21, 0.95]
Safdar 2008	4/23	6/17		2.1 %	0.49 [0.16, 1.48]
Selinger 2011	2/62	5/62		1.1 %	0.40 [0.08, 1.98]
Shimbo 2005	1/18	2/17		0.5 %	0.47 [0.05, 4.74]
Surawicz 1989	41/212	23/106		6.7 %	0.89 [0.57, 1.40]
Thomas 2001	45/156	43/150		8.2 %	1.01 [0.71, 1.43]
Wenus 2008	6/46	11/41		2.9 %	0.49 [0.20, 1.20]



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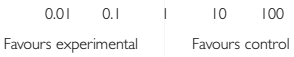
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Total (95% CI)	**2404**	**2177**	♦	**100.0 %**	**0.69 [0.58, 0.82]**
Total events: 365 (Experimental), 455 (Control)					
Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 38.75$, df = 24 (P = 0.03); $I^2 = 38\%$					
Test for overall effect: Z = 4.27 (P = 0.000020)					
Test for subgroup differences: Not applicable					



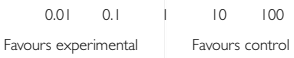
Analysis 5.4. Comparison 5 Antibiotic associated diarrhea, Outcome 4 Incidence AAD: sensitivity (2:1).

Review: Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children

Comparison: 5 Antibiotic associated diarrhea

Outcome: 4 Incidence AAD: sensitivity (2:1)

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Arvola 1999	15/89	13/78		4.4 %	1.01 [0.51, 1.99]
Beausoleil 2007	7/44	16/45		3.7 %	0.45 [0.20, 0.98]
Bravo 2008	4/41	5/45		1.9 %	0.88 [0.25, 3.05]
Can 2006	1/73	7/78		0.8 %	0.15 [0.02, 1.21]
Cindoruk 2007	9/62	19/62		4.2 %	0.47 [0.23, 0.96]
Duman 2005	14/204	28/185		4.9 %	0.45 [0.25, 0.83]
Gao 2010	37/171	37/84		7.0 %	0.49 [0.34, 0.71]
Hickson 2007	12/69	21/66		4.8 %	0.55 [0.29, 1.02]
Imase 2008	1/12	3/7		0.8 %	0.19 [0.02, 1.53]
Koning 2008	9/20	15/21		5.3 %	0.63 [0.36, 1.10]
Kotowska 2005	14/132	31/137		5.1 %	0.47 [0.26, 0.84]
Lewis 1998	8/35	5/38		2.6 %	1.74 [0.63, 4.81]



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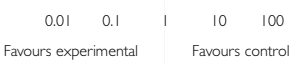
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Lonnermark 2010	22/118	13/121		4.7 %	1.74 [0.92, 3.28]
McFarland 1995	7/97	14/96		3.3 %	0.49 [0.21, 1.17]
Miller 2008b	8/157	4/159		2.1 %	2.03 [0.62, 6.59]
Plummer 2004	20/69	24/69		5.9 %	0.83 [0.51, 1.36]
Pozzoni 2012	31/141	21/134		5.8 %	1.40 [0.85, 2.32]
Psaradellis 2010	54/233	69/239		7.6 %	0.80 [0.59, 1.09]
Ruszczynski 2008	9/120	20/120		3.9 %	0.45 [0.21, 0.95]
Safdar 2008	4/23	6/17		2.3 %	0.49 [0.16, 1.48]
Selinger 2011	2/62	5/62		1.3 %	0.40 [0.08, 1.98]
Shimbo 2005	1/18	2/17		0.7 %	0.47 [0.05, 4.74]
Surawicz 1989	51/212	23/106		6.4 %	1.11 [0.72, 1.71]
Thomas 2001	47/156	43/150		7.2 %	1.05 [0.74, 1.49]
Wenus 2008	7/46	11/41		3.4 %	0.57 [0.24, 1.33]
Total (95% CI)	**2404**	**2177**		**100.0 %**	**0.73 [0.60, 0.88]**

Total events: 394 (Experimental), 455 (Control)

Heterogeneity: $Tau^2 = 0.10$; $Chi^2 = 48.90$, df = 24 (P = 0.002); $I^2 = 51\%$

Test for overall effect: Z = 3.25 (P = 0.0012)

Test for subgroup differences: Not applicable



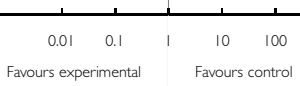
Analysis 5.5. Comparison 5 Antibiotic associated diarrhea, Outcome 5 Incidence AAD: sensitivity (3:1).

Review: Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children

Comparison: 5 Antibiotic associated diarrhea

Outcome: 5 Incidence AAD: sensitivity (3:1)

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Arvola 1999	20/89	13/78		4.7 %	1.35 [0.72, 2.53]
Beausoleil 2007	7/44	16/45		3.9 %	0.45 [0.20, 0.98]
Bravo 2008	4/41	5/45		2.2 %	0.88 [0.25, 3.05]
Can 2006	1/73	7/78		1.0 %	0.15 [0.02, 1.21]
Cindoruk 2007	9/62	19/62		4.2 %	0.47 [0.23, 0.96]
Duman 2005	14/204	28/185		4.8 %	0.45 [0.25, 0.83]
Gao 2010	37/171	37/84		6.2 %	0.49 [0.34, 0.71]
Hickson 2007	14/69	21/66		4.9 %	0.64 [0.35, 1.15]
Imase 2008	1/12	3/7		1.0 %	0.19 [0.02, 1.53]
Koning 2008	10/20	15/21		5.3 %	0.70 [0.42, 1.17]
Kotowska 2005	17/132	31/137		5.2 %	0.57 [0.33, 0.98]
Lewis 1998	8/35	5/38		2.9 %	1.74 [0.63, 4.81]
Lonnermark 2010	30/118	13/121		4.8 %	2.37 [1.30, 4.31]
McFarland 1995	7/97	14/96		3.5 %	0.49 [0.21, 1.17]
Miller 2008b	8/157	4/159		2.4 %	2.03 [0.62, 6.59]
Plummer 2004	20/69	24/69		5.5 %	0.83 [0.51, 1.36]
Pozzoni 2012	38/141	21/134		5.5 %	1.72 [1.07, 2.77]
Psaradellis 2010	58/233	69/239		6.6 %	0.86 [0.64, 1.16]
Ruszczynski 2008	9/120	20/120		4.1 %	0.45 [0.21, 0.95]
Safdar 2008	4/23	6/17		2.7 %	0.49 [0.16, 1.48]
Selinger 2011	2/62	5/62		1.5 %	0.40 [0.08, 1.98]
Shimbo 2005	1/18	2/17		0.8 %	0.47 [0.05, 4.74]
Surawicz 1989	71/212	23/106		5.9 %	1.54 [1.03, 2.32]
Thomas 2001	51/156	43/150		6.3 %	1.14 [0.81, 1.60]
Wenus 2008	9/46	11/41		3.9 %	0.73 [0.34, 1.58]



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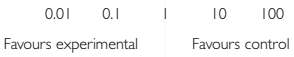
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Total (95% CI)	**2404**	**2177**	◆	**100.0 %**	**0.80 [0.64, 0.99]**
Total events: 450 (Experimental), 455 (Control)					
Heterogeneity: $Tau^2 = 0.18$; $Chi^2 = 68.96$, df = 24 (P<0.00001); I^2 =65%					
Test for overall effect: Z = 2.00 (P = 0.045)					
Test for subgroup differences: Not applicable					



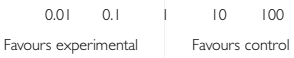
Analysis 5.6. Comparison 5 Antibiotic associated diarrhea, Outcome 6 Incidence AAD: sensitivity (5:1).

Review: Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children

Comparison: 5 Antibiotic associated diarrhea

Outcome: 6 Incidence AAD: sensitivity (5:1)

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Arvola 1999	31/89	13/78		4.8 %	2.09 [1.18, 3.70]
Beausoleil 2007	7/44	16/45		4.0 %	0.45 [0.20, 0.98]
Bravo 2008	4/41	5/45		2.7 %	0.88 [0.25, 3.05]
Can 2006	1/73	7/78		1.3 %	0.15 [0.02, 1.21]
Cindoruk 2007	9/62	19/62		4.3 %	0.47 [0.23, 0.96]
Duman 2005	14/204	28/185		4.6 %	0.45 [0.25, 0.83]
Gao 2010	37/171	37/84		5.4 %	0.49 [0.34, 0.71]
Hickson 2007	19/69	21/66		5.0 %	0.87 [0.51, 1.46]
Imase 2008	1/12	3/7		1.3 %	0.19 [0.02, 1.53]
Koning 2008	10/20	15/21		5.0 %	0.70 [0.42, 1.17]
Kotowska 2005	22/132	31/137		5.1 %	0.74 [0.45, 1.20]
Lewis 1998	9/35	5/38		3.4 %	1.95 [0.72, 5.27]



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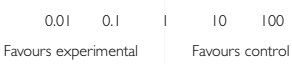
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Lonnermark 2010	44/118	13/121		4.8 %	3.47 [1.97, 6.10]
McFarland 1995	7/97	14/96		3.8 %	0.49 [0.21, 1.17]
Miller 2008b	8/157	4/159		2.8 %	2.03 [0.62, 6.59]
Plummer 2004	20/69	24/69		5.1 %	0.83 [0.51, 1.36]
Pozzoni 2012	51/141	21/134		5.2 %	2.31 [1.47, 3.62]
Psaradellis 2010	64/233	69/239		5.7 %	0.95 [0.71, 1.27]
Ruszczynski 2008	9/120	20/120		4.2 %	0.45 [0.21, 0.95]
Safdar 2008	4/23	6/17		3.0 %	0.49 [0.16, 1.48]
Selinger 2011	2/62	5/62		1.9 %	0.40 [0.08, 1.98]
Shimbo 2005	1/18	2/17		1.1 %	0.47 [0.05, 4.74]
Surawicz 1989	107/212	23/106		5.4 %	2.33 [1.58, 3.42]
Thomas 2001	58/156	43/150		5.6 %	1.30 [0.94, 1.79]
Wenus 2008	14/46	11/41		4.4 %	1.13 [0.58, 2.21]
Total (95% CI)	**2404**	**2177**		**100.0 %**	**0.90 [0.69, 1.18]**

Total events: 553 (Experimental), 455 (Control)

Heterogeneity: $Tau^2 = 0.31$; $Chi^2 = 111.50$, df = 24 (P<0.00001); $I^2 = 78\%$

Test for overall effect: Z = 0.75 (P = 0.45)

Test for subgroup differences: Not applicable

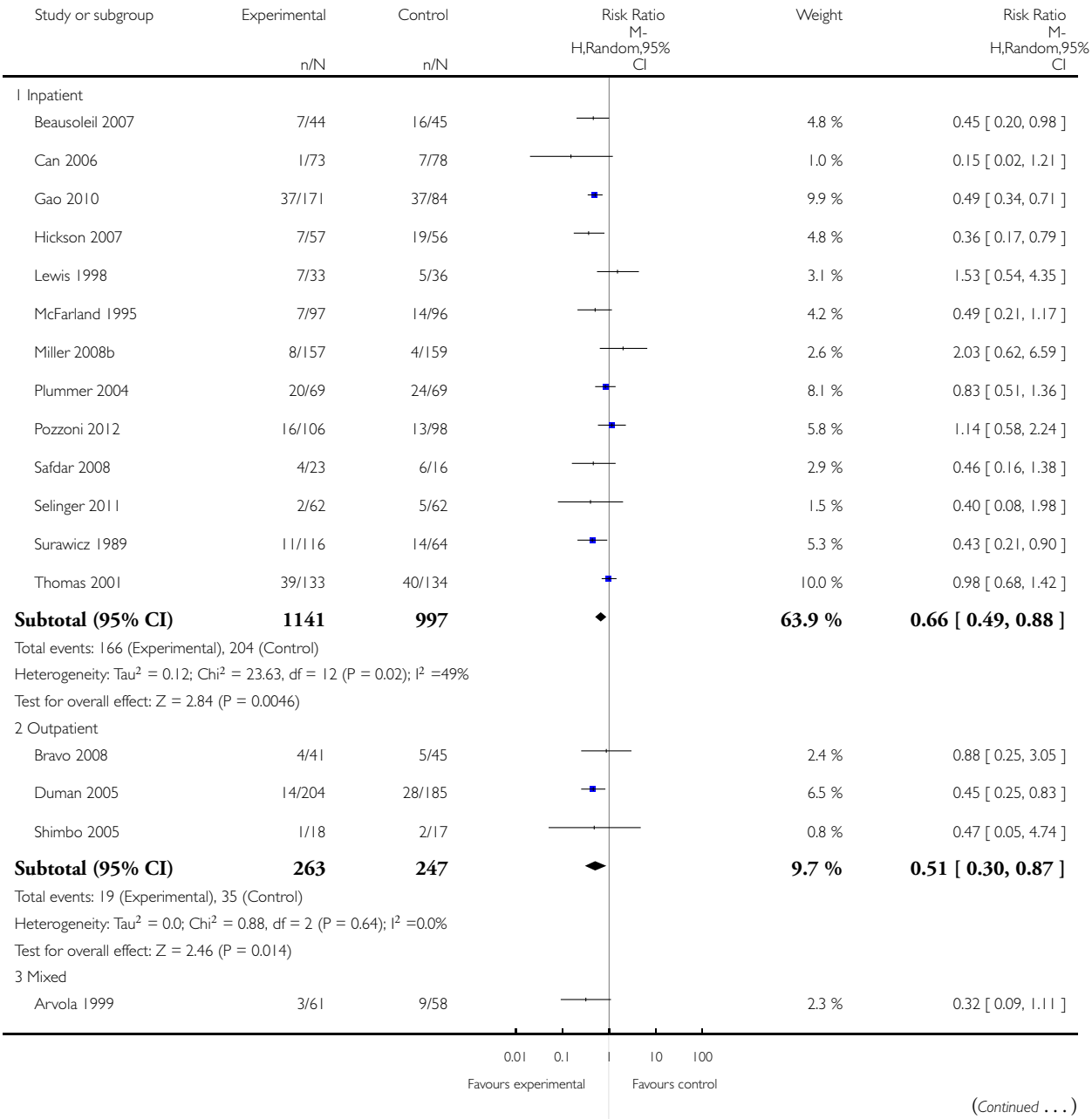


Analysis 5.7. Comparison 5 Antibiotic associated diarrhea, Outcome 7 Patient population.

Review: Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children

Comparison: 5 Antibiotic associated diarrhea

Outcome: 7 Patient population



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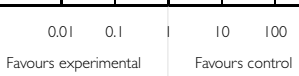
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Kotowska 2005	9/119	29/127		5.5 %	0.33 [0.16, 0.67]
Lonnermark 2010	6/80	5/83		2.7 %	1.25 [0.40, 3.92]
Psaradellis 2010	47/216	65/221		10.8 %	0.74 [0.53, 1.02]
Ruszczynski 2008	9/120	20/120		5.1 %	0.45 [0.21, 0.95]
Subtotal (95% CI)	**596**	**609**		**26.4 %**	**0.55 [0.35, 0.86]**
Total events: 74 (Experimental), 128 (Control)					
Heterogeneity: Tau^2 = 0.11; Chi^2 = 7.50, df = 4 (P = 0.11); I^2 =47%					
Test for overall effect: Z = 2.62 (P = 0.0087)					
Total (95% CI)	**2000**	**1853**		**100.0 %**	**0.62 [0.50, 0.76]**
Total events: 259 (Experimental), 367 (Control)					
Heterogeneity: Tau^2 = 0.08; Chi^2 = 33.15, df = 20 (P = 0.03); I^2 =40%					
Test for overall effect: Z = 4.48 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 0.88, df = 2 (P = 0.64), I^2 =0.0%					

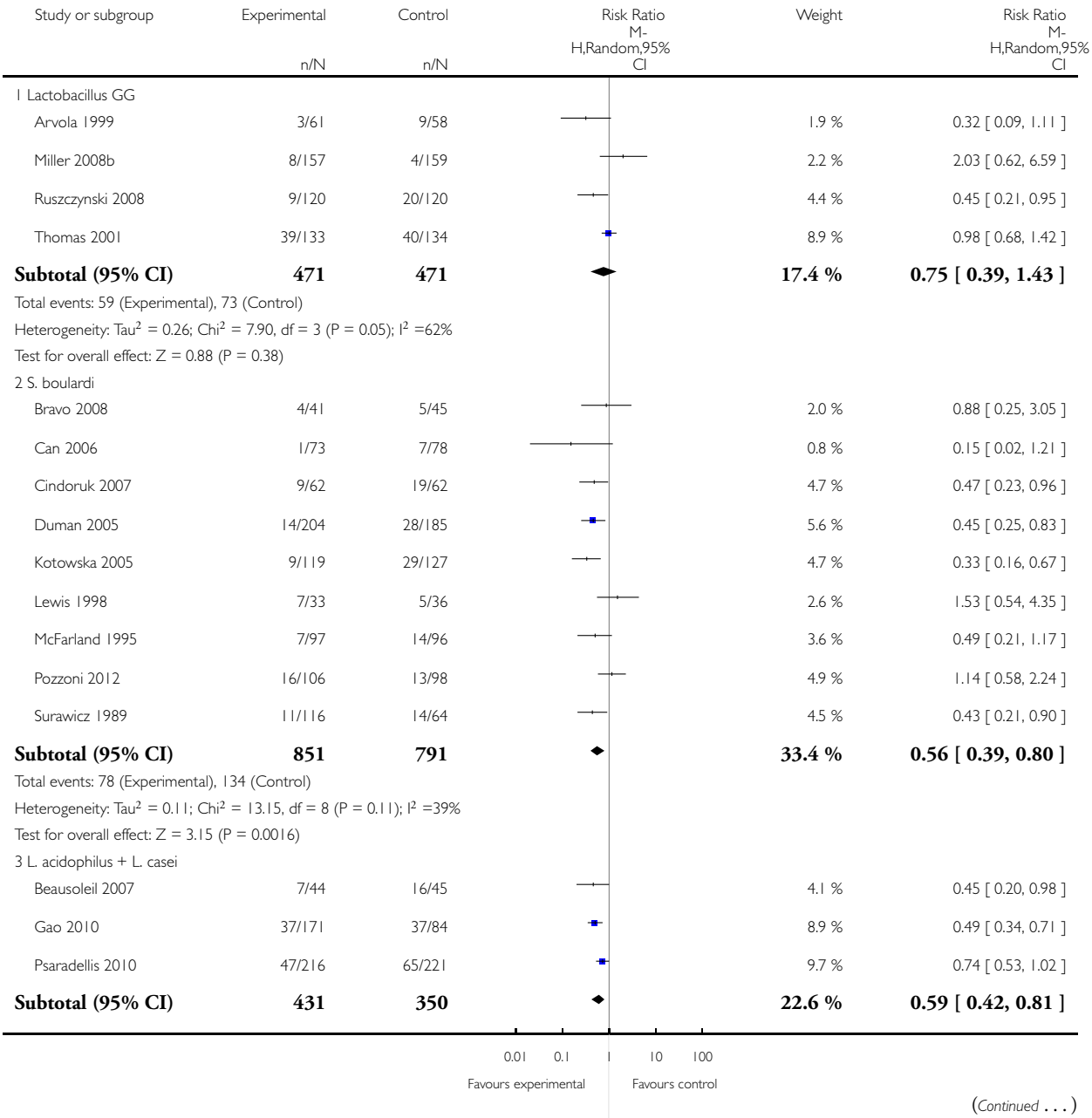


Analysis 5.8. Comparison 5 Antibiotic associated diarrhea, Outcome 8 Species: all.

Review: Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children

Comparison: 5 Antibiotic associated diarrhea

Outcome: 8 Species: all



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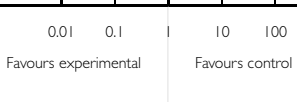
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Total events: 91 (Experimental), 118 (Control)					
Heterogeneity: Tau² = 0.03; Chi² = 3.24, df = 2 (P = 0.20); I² =38%					
Test for overall effect: Z = 3.26 (P = 0.0011)					
4 Clostridium butyricum					
Imase 2008	1/12	3/7		0.8 %	0.19 [0.02, 1.53]
Shimbo 2005	1/18	2/17		0.6 %	0.47 [0.05, 4.74]
Subtotal (95% CI)	**30**	**24**		**1.4 %**	**0.29 [0.06, 1.34]**
Total events: 2 (Experimental), 5 (Control)					
Heterogeneity: Tau² = 0.0; Chi² = 0.32, df = 1 (P = 0.57); I² =0.0%					
Test for overall effect: Z = 1.59 (P = 0.11)					
5 L. acidophilus + B. bifidum					
Plummer 2004	20/69	24/69		7.1 %	0.83 [0.51, 1.36]
Subtotal (95% CI)	**69**	**69**		**7.1 %**	**0.83 [0.51, 1.36]**
Total events: 20 (Experimental), 24 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.73 (P = 0.47)					
6 L. acidophilus					
Safdar 2008	4/23	6/16		2.5 %	0.46 [0.16, 1.38]
Subtotal (95% CI)	**23**	**16**		**2.5 %**	**0.46 [0.16, 1.38]**
Total events: 4 (Experimental), 6 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.38 (P = 0.17)					
7 B. breve + B. longum + B. infantis + L. acidophilus + L. plantarum					
Selinger 2011	2/62	5/62		1.3 %	0.40 [0.08, 1.98]
Subtotal (95% CI)	**62**	**62**		**1.3 %**	**0.40 [0.08, 1.98]**
Total events: 2 (Experimental), 5 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.12 (P = 0.26)					
8 L. casei + L. bulgaris + S. thermophilus					
Hickson 2007	7/57	19/56		4.1 %	0.36 [0.17, 0.79]
Subtotal (95% CI)	**57**	**56**		**4.1 %**	**0.36 [0.17, 0.79]**
Total events: 7 (Experimental), 19 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.54 (P = 0.011)					
9 L. plantarum					
Lonnermark 2010	6/80	5/83		2.3 %	1.25 [0.40, 3.92]
Subtotal (95% CI)	**80**	**83**		**2.3 %**	**1.25 [0.40, 3.92]**
Total events: 6 (Experimental), 5 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.37 (P = 0.71)					
10 Lactobacillus GG + L. acidophilus + B. animalis					



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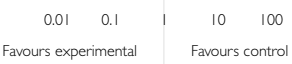
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Wenus 2008	2/34	8/29		1.5 %	0.21 [0.05, 0.93]
Subtotal (95% CI)	**34**	**29**		**1.5 %**	**0.21 [0.05, 0.93]**
Total events: 2 (Experimental), 8 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.06 (P = 0.039)					
11 B. bifidum + B. lactis + B. longum + E. faecium + L. acidophilus + L. paracasei + L. plantarum + L. rhamnosus + L. sativarius					
Koning 2008	9/19	15/19		6.6 %	0.60 [0.35, 1.02]
Subtotal (95% CI)	**19**	**19**		**6.6 %**	**0.60 [0.35, 1.02]**
Total events: 9 (Experimental), 15 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.90 (P = 0.058)					
Total (95% CI)	**2127**	**1970**		**100.0 %**	**0.60 [0.49, 0.72]**
Total events: 280 (Experimental), 412 (Control)					
Heterogeneity: Tau^2 = 0.07; Chi^2 = 37.30, df = 24 (P = 0.04); I^2 =36%					
Test for overall effect: Z = 5.34 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 8.69, df = 10 (P = 0.56), I^2 =0.0%					

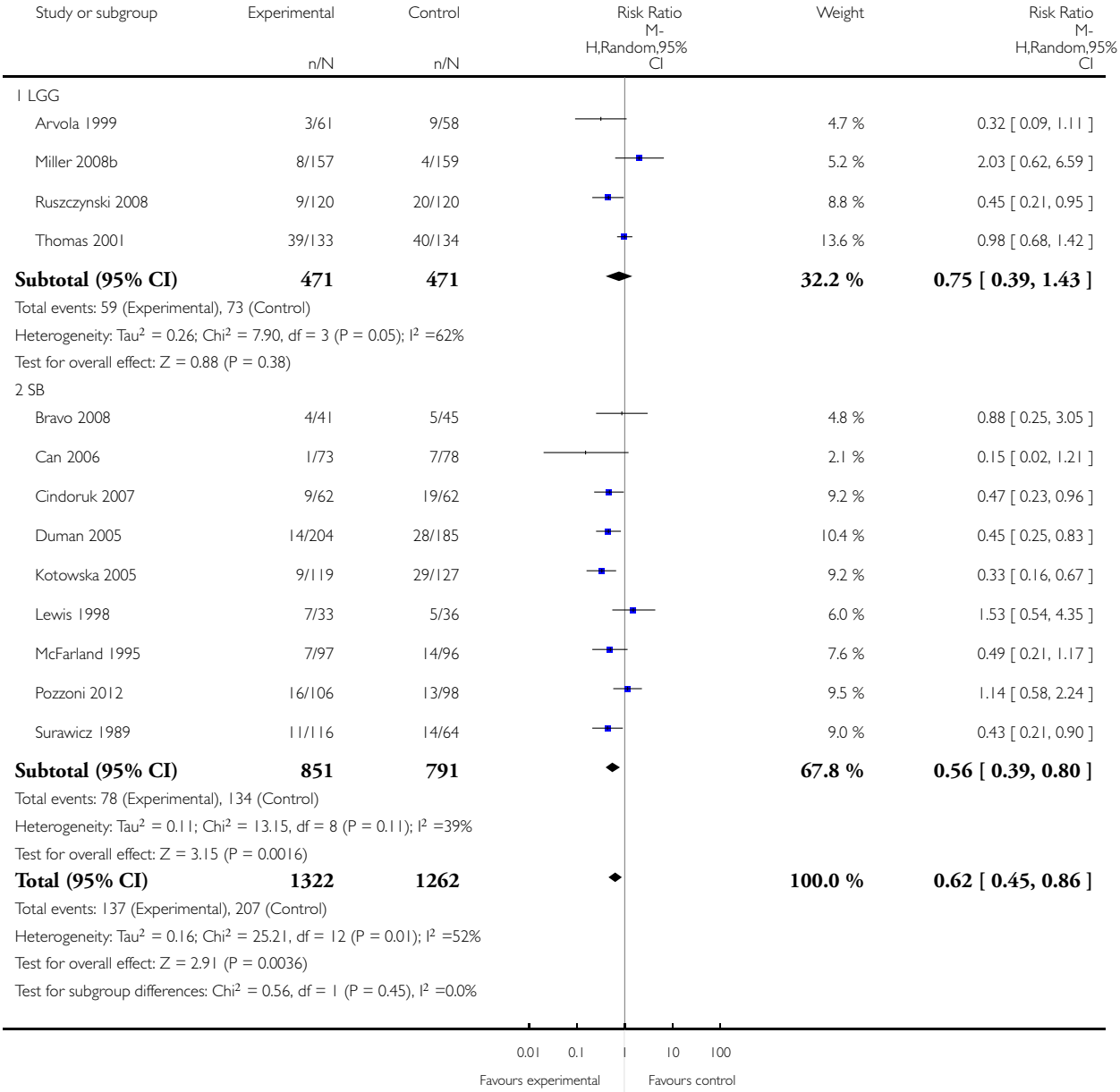


Analysis 5.9. Comparison 5 Antibiotic associated diarrhea, Outcome 9 Species: LGG versus SB.

Review: Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children

Comparison: 5 Antibiotic associated diarrhea

Outcome: 9 Species: LGG versus SB

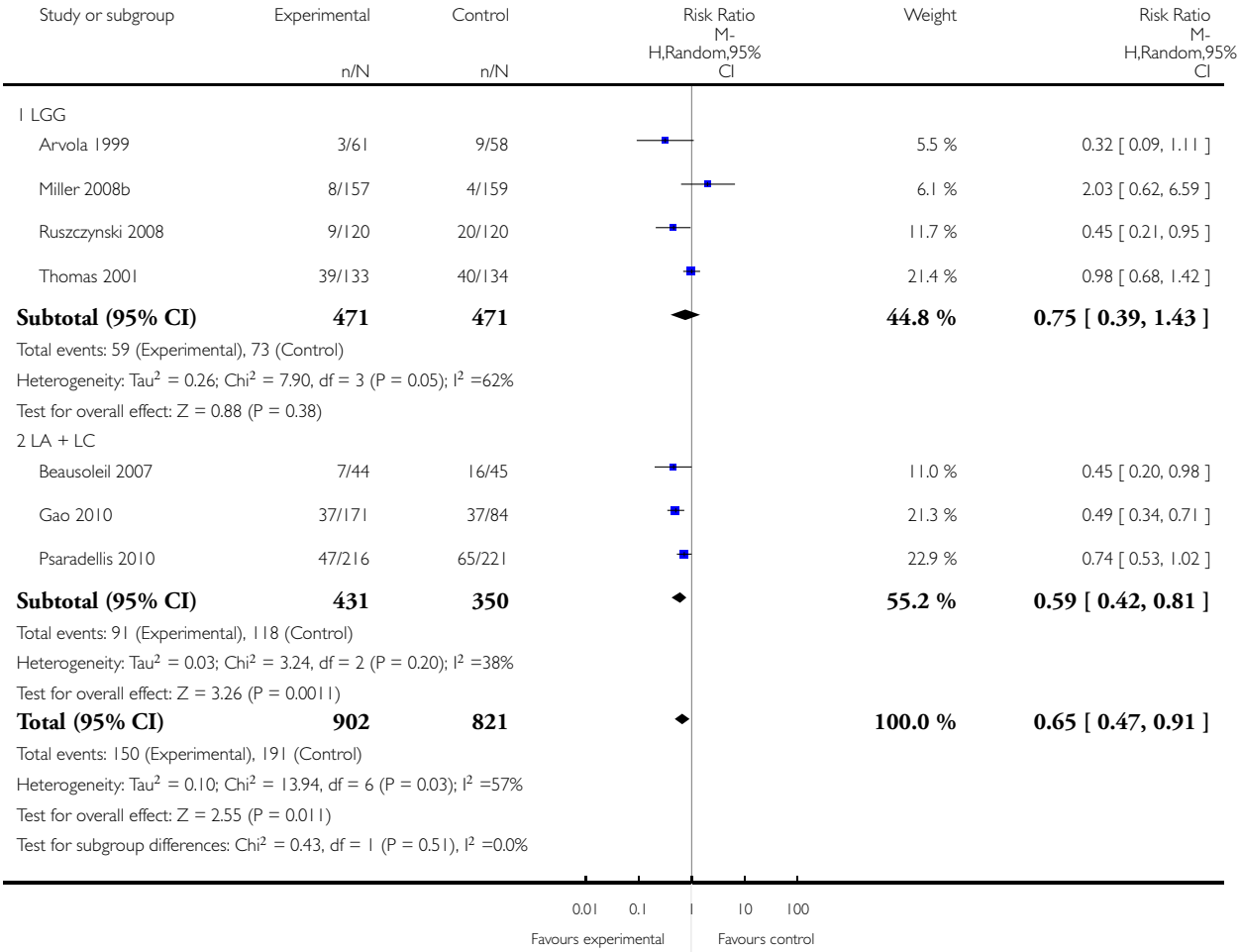


Analysis 5.10. Comparison 5 Antibiotic associated diarrhea, Outcome 10 Species: LGG versus LA + LC.

Review: Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children

Comparison: 5 Antibiotic associated diarrhea

Outcome: 10 Species: LGG versus LA + LC

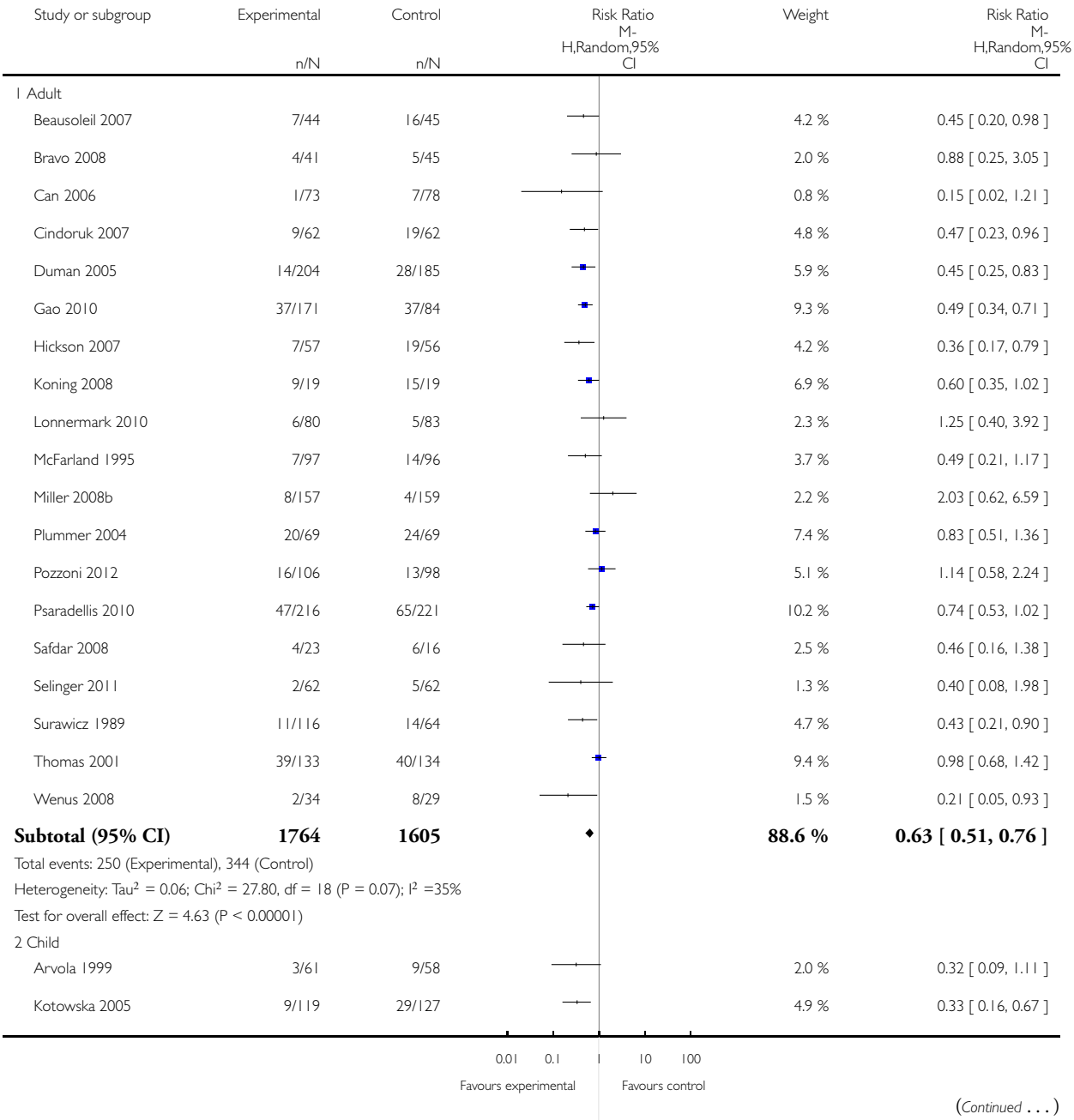


Analysis 5.11. Comparison 5 Antibiotic associated diarrhea, Outcome 11 Adult versus child.

Review: Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children

Comparison: 5 Antibiotic associated diarrhea

Outcome: 11 Adult versus child



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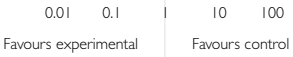
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Ruszczynski 2008	9/120	20/120		4.5 %	0.45 [0.21, 0.95]
Subtotal (95% CI)	**300**	**305**		**11.4 %**	**0.37 [0.23, 0.60]**
Total events: 21 (Experimental), 58 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.42$, df = 2 (P = 0.81); $I^2 = 0.0\%$					
Test for overall effect: Z = 4.08 (P = 0.000045)					
Total (95% CI)	**2064**	**1910**		**100.0 %**	**0.59 [0.49, 0.71]**
Total events: 271 (Experimental), 402 (Control)					
Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 33.21$, df = 21 (P = 0.04); $I^2 = 37\%$					
Test for overall effect: Z = 5.43 (P < 0.00001)					
Test for subgroup differences: $Chi^2 = 3.92$, df = 1 (P = 0.05), $I^2 = 75\%$					



APPENDICES

Appendix 1. EMBASE search strategy

#1 'probiotic agent'/exp OR 'probiotic agent' OR probio* OR 'dairy product':de OR 'yoghurt'/exp OR yoghurt OR 'yogurt'/exp OR yogurt OR 'kefir'/exp OR kefir OR 'fermented product'/exp OR 'fermented product'

#2 'lactobacillus'/exp OR lactobacillus OR lactobacill* OR l AND acidophilus OR l AND casei OR l AND delbrueckii OR l AND helveticus OR l AND johnsonii OR l AND paracasei OR l AND plantarum OR l AND reuteri OR l AND rhamnosus OR l AND salivarius

#3 saccharomyce* OR 'streptococcus'/exp OR streptococcus AND thermophilus OR 'clostridium'/exp OR clostridium AND butyricum OR 'enterococcus'/exp OR enterococcus AND faecium OR 'antibiosis'/exp OR antibiosis OR biotherapeutic AND agent*

#4 'bifidobacterium'/exp OR bifidobacterium OR bifidobacter* OR b AND animalis OR b AND bifidum OR b AND breve OR b AND infantis OR b AND lactis OR b AND longum

#5 #1 OR #2 OR #3 OR #4

#6 'anti-bacterial agents':de OR antimicrobial* OR antibiotic* OR 'antimicrobial'/exp OR antimicrobial OR 'anti microbial' OR antimycobacteri* OR antibacteri* OR bacteriocid* NEAR/1 agent*

#7 'clostridium difficile infection':de OR 'clostridium'/exp OR clostridium AND difficile OR c AND diff OR 'clostridium difficile associated' NEXT/1 diarrhea OR 'disease'/exp OR disease OR 'colitis'/exp OR colitis OR infections OR 'clostridium difficile toxin a'/exp OR 'clostridium difficile toxin a' OR 'clostridium difficile toxin b'/exp OR 'clostridium difficile toxin b' OR 'diarrhea'/exp OR diarrhea OR diarrhea* OR diarrhoe* OR diarhe* OR diarhoe* OR dysenter* OR gastroenteritis* OR 'gastro'/exp OR gastro AND enteritis*

#8 random* OR factorial* OR crossover* OR cross AND over* OR placebo* OR doubl* OR singl* NEXT/1 blind* OR assign* OR allocate* OR volunteer* OR 'crossover procedure'/exp OR 'crossover procedure' OR 'double blind procedure'/exp OR 'double blind procedure' OR 'randomized controlled trial'/exp OR 'randomized controlled trial' OR 'single blind procedure'/exp OR 'single blind procedure'

#9 #5 AND #6 AND #7 AND #8

CONTRIBUTIONS OF AUTHORS

Joshua Goldenberg: Inclusion/exclusion, data extraction, quality assessment, data analysis, manuscript preparation, administrative and technical support, critical revision of article

Stephanie Ma: Screening, inclusion/exclusion, data extraction

Jane Saxton: Search strategy, manuscript preparation, critical revision of article

Mark Martzen: Screening, inclusion/exclusion, data extraction

Per Vandvik: Quality assessment, manuscript preparation, critical revision of article

Kristian Thorlund: Developed review protocol, data analysis, manuscript preparation

Gordon Guyatt: Quality assessment, manuscript preparation, critical revision of article

Bradley Johnston: Concept, developed review protocol, screening, inclusion/exclusion, data extraction, quality assessment, data analysis, manuscript preparation, critical revision of article

DECLARATIONS OF INTEREST

None known

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Internal sources

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External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The secondary outcomes of mortality, need of antibiotics to treat *C. difficile* infection, and recurrence of *C. difficile* infection were not evaluated due to inadequate number of studies with this data. In addition to funnel plots we used the Harbord linear regression method to detect small study effect in view of recently proposed guidelines.

INDEX TERMS

Medical Subject Headings (MeSH)

*Clostridium difficile; Anti-Bacterial Agents [*adverse effects]; Diarrhea [microbiology; *prevention & control]; Enterocolitis, Pseudomembranous [*complications]; Probiotics [*therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Child; Humans