

BMJ Open Probiotics for the prevention of antibiotic-associated diarrhoea: a systematic review and meta-analysis

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ABSTRACT

Objective To evaluate existing evidence for the use of probiotics in preventing antibiotic-associated diarrhoea (AAD) in adults.

Design Systematic review and meta-analysis of randomised controlled trials (RCTs).

Data sources We performed a literature search of the electronic databases CINAHL Plus, EMBASE, MEDLINE (Ovid) and Web of Science from database inception to May 2021 as well as hand searching of trial registries and reference lists of related reviews.

Study selection Two reviewers identified whether RCTs met the following inclusion criteria: adult population to whom antibiotics were administered; a probiotic intervention; a placebo, alternative dose, alternative probiotic strain or no treatment control; and incidence of AAD as the outcome.

Data extraction and synthesis Two reviewers independently collected data and assessed risk of bias using preconstructed data extraction forms. We used a random effects model for all analyses. Subgroup analyses were performed to evaluate species-specific and dose-specific response.

Results Forty-two studies (11,305 participants) were included in this review. The pooled analysis suggests that co-administration of probiotics with antibiotics reduces the risk of AAD in adults by 37% (risk ratio (RR)=0.63 (95% CI 0.54 to 0.73), $p<0.00001$). The overall quality of the evidence using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) criteria was found to be moderate. In subgroup analyses, high dose compared with low dose of the same probiotic demonstrated a positive protective effect (RR 0.54 (95% CI 0.38 to 0.76), $p<0.01$), and only certain species, mainly of the lactobacillus and bifidobacteria genera, were found to be effective. Studies with a low baseline AAD risk did not show any difference in risk but studies with moderate or high baseline AAD risk demonstrated a significant risk reduction.

Conclusions Probiotics are effective for preventing AAD. Secondary analyses of higher dosages and certain species have shown increased effectiveness. Our results may not be applicable in clinical scenarios of lower baseline AAD risk.

INTRODUCTION

Antibiotics are one of the most prescribed medications worldwide. They disturb normal gastrointestinal microbiota¹ and a common consequence is diarrhoea.² This leads to

Strengths and limitations of this study

- An updated literature search encapsulating 4 years of new data since a comparable meta-analysis was last published by Cochrane in 2017.
- We calculated and reported the number needed to be treated with probiotics to protect one person from antibiotic-associated diarrhoea (AAD), so that our data can be easily interpreted by patients and clinicians.
- This meta-analysis looked only at incidence of AAD, but clinical applicability may have been improved by collecting data on duration and severity of AAD as well as length of stay in hospital and quality of life measures.
- There was complexity in combining results due to substantial heterogeneity between study methodologies and outcome measures.

prolonged hospital admissions,³ increased morbidity and mortality,⁴ and greater costs to the health system.^{5,6} Antibiotic-associated diarrhoea (AAD) has been reported in 5%–35% of patients receiving antibiotics, varying with the type of antibiotics, the general health of the patient and their exposure to pathogens.⁷

Probiotics are live micro-organisms that, when administered in adequate amounts, confer a health benefit on the host.⁸ They are believed to improve the microbial balance of the host and reduce colonisation by pathogenic bacteria. They can be delivered orally, are thought to adhere to target gastrointestinal epithelium and are stable in acid and bile.⁹ Probiotics are increasingly available in capsules, powders and fermented milk drinks and are promoted in health food shops and supermarkets, and in the media, for a multitude of purposes.

Several mechanisms are proposed to contribute to the protective effect of probiotics against AAD. Antibiotics are known to disrupt the complex balance of gastrointestinal microbiota, allowing colonisation by pathogenic organisms such as *Clostridium*

difficile. Probiotics are believed to temporarily colonise the gut, producing bactericidal acids and peptides, and competing for nutrients and epithelial adhesion. Several species of the *Lactobacillus* genus are acid producing, lower environmental pH, and secrete exotoxins that inhibit pathogenic bacterial growth and inhibit binding of enterotoxins to gut epithelium.^{10–13} Probiotics, particularly species in the *Lactobacillus* and *Saccharomyces* genera, are also reported to upregulate both the innate and adaptive immune systems through multiple mechanisms.^{14–17}

It is suggested that probiotics are the panacea to AAD. This would be a very attractive solution to an expensive problem with significant morbidity. It is estimated that the increase in length of hospital stay due to AAD is 3.6–21.3 days.^{18 19} One of the most expensive probiotics in Australia costs less than nine dollars daily (VSL#3 probiotic formulation, \$A8.60 per day, April 2021). This is negligible compared with the cost of 1 day of Australian hospital inpatient care, which according to 2017 data, cost on average \$A2128.²⁰

Our hypothesis has been extensively investigated. In a Cochrane review²¹ authors found moderate quality evidence for a large protective effect of probiotics against *C. difficile*-associated diarrhoea (CDAD) (RR 0.40, 95% CI 0.30 to 0.52). Although *C. difficile* is the most common infectious organism isolated, in most cases of AAD no causative agent is found. Faecal analysis indicates incidence of *C. difficile* in AAD to be 20%,²² or less.²³ Furthermore, while probiotics significantly reduce incidence of CDAD they do not appear to reduce *C. difficile* infection.²¹ Goldenberg and colleagues suggest that the role of probiotics may be more in alleviating the symptoms of infection rather than preventing colonisation itself.²¹ For this reason, we examined the protective effect of probiotics on the occurrence of AAD without any specific causative organism.

The primary objective of this systematic review and meta-analysis was to evaluate existing evidence for the protective effect of probiotics against AAD in adults. Secondary objectives were to examine dose–response and species-specific response in preventing AAD.

METHODS

Eligibility criteria

Randomised controlled trials (RCTs) comparing probiotic use (any strain, dose or formulation) to placebo, alternative dose, alternative probiotic strain or no treatment, for the prevention of diarrhoea in adults receiving antibiotic therapy, were eligible for inclusion in this review. Studies of adults, receiving any antibiotic therapy for a course of any length, or for any reason, were included. Studies of paediatric populations were excluded. The primary outcome measure was incidence of AAD, as defined by authors, during the antibiotic treatment or follow-up phases. Studies were excluded if they examined probiotics only for treatment, rather than prevention, of AAD.

We limited included studies to those written in English as our group did not speak any other languages.

Information sources and search strategy

A comprehensive electronic title search (online supplemental file 1) was performed of CINAHL Plus, EMBASE, MEDLINE (Ovid), Web of Science and Google Scholar from database inception to May 2021. The search was broad to include as many individual probiotic species as possible and all clinical indications or outcomes (full search terms in Appendix A). Grey literature and clinical trial registers including ClinicalTrials.gov and the Australia New Zealand Clinical Trials Registry (ANZCTR) were searched, as well as hand searching of reference lists of relevant systematic reviews and included studies. The search was limited to RCTs in an adult population.

Study selection

Two of three of the authors (CG, GK and KL) independently assessed each study for inclusion in the review. Discrepancies were resolved through discussion.

Data collection process and data items

Data were extracted from each article by two of three of the authors (CG, GK, KL), using a standardised data extraction form following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.²⁴ This was housed within Covidence online software (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia; available at www.covidence.org). Data items collected included the number of patients allocated to each group, the probiotic species, formulation, dose and regime, whether a placebo or ‘nothing’ control was used, and outcome data on incidence of AAD.

Assessment of risk of bias in individual studies and overall quality of the evidence

The risk of bias was assessed using the Cochrane Risk of Bias²⁵ tool within the Covidence online software. The domains 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 (eg, differences in baseline characteristics or funding of trials by pharmaceutical companies). Assessment was conducted by two of three authors (CG, GK, KL) and discrepancies resolved by consensus. The overall quality of the evidence was rated using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach²⁶ independently by two authors (CG, KL) and consensus reached through discussion.

Statistical analysis and measures of treatment effect

For data analysis we used the RevMan V.5.4.1 statistical software (Review Manager (RevMan) (Computer program), V.5.4, The Cochrane Collaboration, 2020). Using a random-effects model, dichotomous data were reported as a risk ratio (RR) with corresponding 95% CIs. The

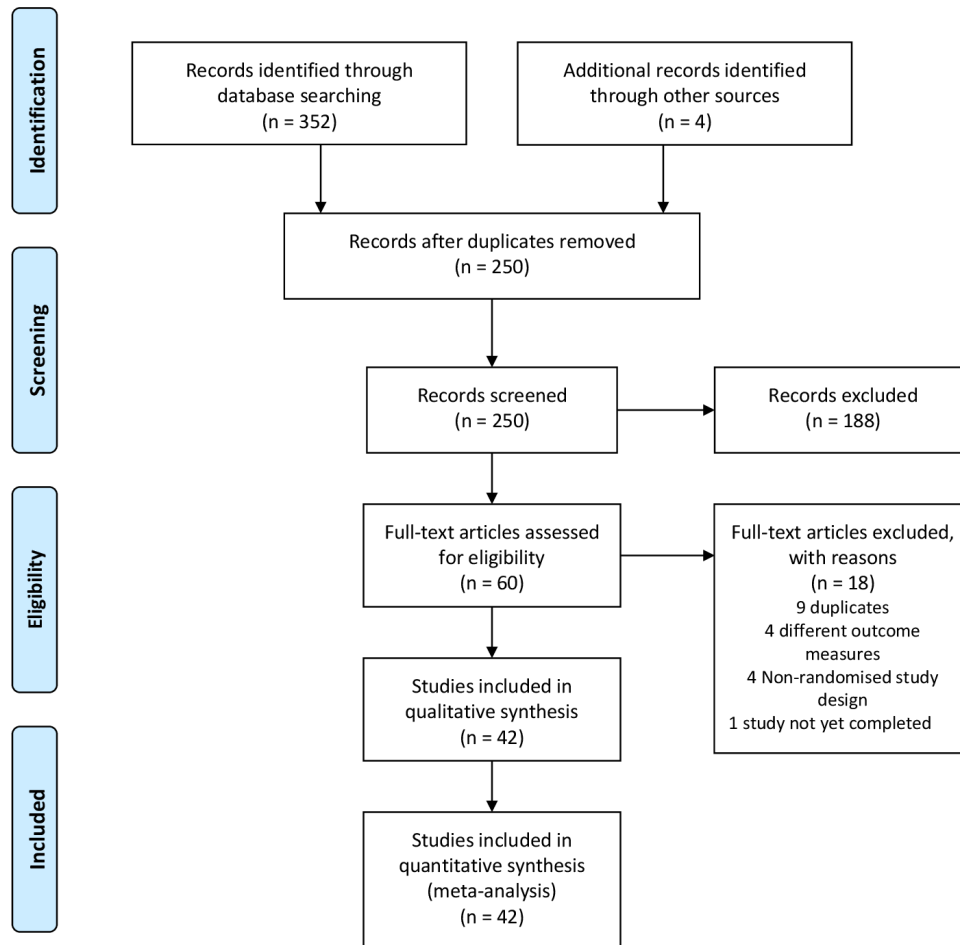


Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram depicting the phases of this systematic review. A total of 352 articles were identified in the initial search, 250 remained after removal of duplicates, of which 60 were eligible for full-text review and 42 of those articles were eligible for inclusion in the study.²⁴

number needed to treat (NNT) was also calculated for the complete case analysis. The I^2 statistic was reported for statistical heterogeneity, although clinical and methodological heterogeneity would not have been reflected within this test. Our *a priori* clinical heterogeneity variables included: probiotic dose, probiotic species and risk of bias. We also conducted *post hoc* subgroup analyses on baseline risk for our primary outcome, incidence of AAD, and concurrent use of probiotics with *H. pylori* eradication. Sensitivity analyses were performed where deemed necessary.

Patient and public involvement

There was no patient or public involvement in this study.

RESULTS

Study selection and characteristics

A total of 356 articles were identified in the initial search, of which 60 were eligible for full-text review, and 42 of those articles (11 305 participants) were eligible for inclusion in the study. Five of these were published after the Cochrane review mentioned previously.²¹ Figure 1 summarises the PRISMA flow of studies. The characteristics of each included study are presented in table 1.

All included studies were RCTs, conducted in adult populations. The overall age range was from 15 to 85 years. Interventions were comparable, in terms of all being probiotics, however, there was variation in the dose and species of probiotic used as well as the probiotic formulation ie, tablets, powder, yoghurt or fermented milk drink. We investigated these by subgroup analysis. All included studies reported on the outcome of interest; incidence of AAD. However, this was measured differently between studies and was not the primary research question of the trial in all cases.

Risk of bias within studies

The risk of bias summary is displayed in figure 2. Six of the 42 studies were rated as having a low risk of bias, while 36 were rated as having a high or unclear risk of bias. On sensitivity analysis, the low risk of bias studies demonstrated no protective effect of probiotics (RR=0.78 (95% CI 0.57 to 1.07), $p=0.13$) as opposed to the high or unknown risk of bias studies (RR=0.59 (95% CI 0.50 to 0.70), $p<0.00001$).

Results of individual studies and synthesis of results

Of the 42 studies included (table 1), 33 were placebo-controlled and eight provided ‘no treatment’ as the

Table 1 Characteristics of included studies							
Reference	Total participants (N probiotic: N control)	Healthcare setting and age of patients	Probiotic species	Daily probiotic dose (cfu)	Duration of probiotic therapy	Control	Outcome (AAD) measurement
Allen et al ⁴¹	2941 (1470:1471)	Inpatient ≥65	<i>L. acidophilus</i> , <i>B. bifidum</i>	60×10 ⁹	21 days	Placebo	≥3 loose stools (5–7 Bristol Stool Scale) in 24 hours
Beausoleil et al ⁴²	89 (44:45)	Inpatient 54–85	<i>L. acidophilus</i> , <i>L. casei</i> (Bio-K+CL1285, Bio-K+International, Canada)	50×10 ⁹	Duration of antibiotic	Placebo	≥3 loose stools (5–7 Bristol Stool Scale) in 24 hours
Beniwal et al ⁴³	202 (105:97)	Inpatient >18	<i>L. acidophilus</i> , <i>L. bulgaricus</i> , <i>S. thermophilus</i>	0.002×10 ⁹	8 days	Nothing	>2 loose stools per day
Bravo et al ⁴⁴	86 (41:45)	Outpatient >15	<i>S. boulardii</i>	10.2×10 ⁹	12 days	Placebo	≥3 loose stools per day for ≥2 days
Can et al ³⁵	151 (73:78)	Inpatient 25–50	<i>S. boulardii</i>	Not noted	Not noted	Placebo	Not noted
Chatterjee et al ⁴⁵	343 (176:167)	Outpatient >18	<i>L. acidophilus</i> LA-5, <i>B. animalis</i> ssp lactis BB-12	4×10 ⁹	Duration of antibiotic	Placebo	≥3 loose stools (5–7 Bristol Stool Scale) for ≥2 days
Cimperman et al ⁴⁶	23 (13:10)	Inpatient >18	<i>L. reuteri</i> ATCC 55730 (BioGaia Biologics, Sweden)	0.2×10 ⁹	28 days	Placebo	≥3 loose stools (5–7 Bristol Stool Scale) for ≥2 days
Cindoruk et al ⁴⁷	124 (62:62)	Inpatients being treated for <i>H. pylori</i>	<i>S. boulardii</i>	1 g (cfu not noted)	14 days	Placebo	Not noted
de Vrese et al ³³	88 (30:29:29) (probiotic:pasteurised: acidified)	Outpatients being treated for <i>H. pylori</i>	<i>L. acidophilus</i> , LA-5, <i>B. animalis</i> ssp lactis, BB-12, <i>S. thermophilus</i>	0.25×10 ⁹	56 days	Pasteurised and acidified placebos	≥3 watery stools in 1 day
Duman et al ⁴⁸	389 (204:185)	Outpatients being treated for <i>H. pylori</i>	<i>S. boulardii</i>	1 g (cfu not noted)	14 days	Nothing	≥3 loose stools per day for ≥2 consecutive days
Ehrhardt et al ⁴⁹	477 (246:231)	Inpatient 40–77	<i>S. boulardii</i>	36×10 ⁹	Duration of antibiotic+7 days	Placebo	≥3 loose stools (5–7 Bristol Stool Scale) in 24 hours
Evans et al ⁵⁰	160 (80:80)	Healthy outpatients 18–50	<i>L. helveticus</i> + <i>L. rhamnosus</i>	4×10 ⁹	Duration of antibiotic+7 days	Placebo	≥3 loose stools (5–7 Bristol Stool Scale) in 24 hours
Gao et al ²⁸	255 (86:85:84) (high:low:placebo)	Inpatient 50–70	<i>L. acidophilus</i> CL1285, <i>L. casei</i> LBC80R	100×10 ⁹ , 50×10 ⁹	Duration of antibiotic+7 days	Placebo	≥3 loose stools (5–7 Bristol Stool Scale) in 24 hours

Continued

Table 1 Continued

Reference	Total participants (N probiotic: N control)	Healthcare setting and age of patients	Probiotic species	Daily probiotic dose (cfu)	Duration of probiotic therapy	Control	Outcome (AAD) measurement
Gotz et al ⁶¹	79 (36:43)	Inpatient >18	<i>L. acidophilus</i> (gasseri), <i>L. helveticus</i> (bulgaricus) (Lactinex)	4×10 ⁹	5 days	Placebo	≥3 stools more than normal number of evacuations in 24 hours
Helps et al ⁶²	85 (44:41)	Inpatient >18	<i>L. casei</i> Shirota (Yakult)	6.5×10 ⁹	Duration of antibiotic+7 days	Placebo	≥3 loose stools in 24 hours
Hickson et al ⁶³	113 (57:56)	Inpatient >50	<i>L. casei</i> defensins, <i>L. bulgaricus</i> , <i>S. thermophilus</i> (Actimel)	0.21×10 ⁹	Duration of antibiotic+5 days	Placebo	≥3 loose stools (5–7 Bristol Stool Scale) in 24 hours
Horosheva et al ²³	271 (91:90:90) (species 1: species 2: placebo)	Outpatient ≥45	(1) <i>B. subtilis</i> 3 and <i>B. licheniformis</i> 31, (2) <i>B. licheniformis</i> only	4×10 ⁹	Duration of antibiotic+7 days	Placebo	≥3 loose stools (5–7 Bristol Stool Scale) for ≥2 days
Iamharit et al ⁶⁴	46 (26:20)	Inpatient	Lyophilized live <i>L. acidophilus</i> + <i>B. bifidum</i> (Inflozan)	6×10 ⁹	14 days	Placebo	≥3 loose stools per day for ≥2 consecutive days or ≥5 loose stools in a day
Imase et al ²⁹	19 (5:7:7) (high:low:nothing)	Inpatients being treated for <i>H. pylori</i>	<i>C. butyricum</i> (CMB588)	0.02×10 ⁹ , 0.01×10 ⁹	7 days	Nothing	Loose or mostly loose stools
Khanal et al ⁶⁵	40 (20:20)	Outpatients undergoing treatment for <i>H. pylori</i>	<i>S. boulardii</i> , <i>Lactobacillus</i> and <i>B. longum</i>	5×10 ⁹	14 days	Nothing	≥3 loose stools per day
Koning et al ⁶⁶	38 (19:19)	Healthy 18–65	<i>B. bifidum</i> W23, <i>B. lactis</i> W18, <i>B. longum</i> W51, <i>E. faecium</i> W54, <i>L. acidophilus</i> W37 and W55, <i>L. paracasei</i> W72, <i>L. plantarum</i> W62, <i>L. rhamnosus</i> W71, <i>L. salivarius</i> W24	2×10 ⁹	14 days	Placebo	≥3 loose stools (5–7 Bristol Stool Scale) in 24 hours
Lewis et al ⁶⁷	69 (33:36)	Inpatient >18	<i>S. boulardii</i>	Not noted	Duration of antibiotic	Placebo	≥3 loose stools (on simplified Bristol Stool Scale) in 24 hours
Lönnemark et al ⁶⁸	163 (80:83)	Inpatient >16	<i>L. plantarum</i> 299v	10×10 ⁹	Duration of antibiotic+7 days	Placebo	≥3 loose stools (5–7 Bristol Stool Scale) for ≥2 days
McFarland et al ⁶⁹	193 (97:96)	Inpatient >18	<i>S. boulardii</i>	Not noted	Duration of antibiotic+3 days	Placebo	≥3 loose stools (5–7 Bristol Stool Scale) for ≥2 days

Continued

Table 1 Continued

Reference	Total participants (N probiotic; N control)	Healthcare setting and age of patients	Probiotic species	Daily probiotic dose (cfu)	Duration of probiotic therapy	Control	Outcome (AAD) measurement
Ouwehand <i>et al</i> ⁶⁰	503 (168:168;167) (high:low;placebo)	Inpatient 30–70	<i>L. acidophilus</i> NCFM (ATCC700396), <i>L. paracasei</i> Lpc-37 (ATCC SD5275), <i>B. lactis</i> Bi-07 (ATCC SD5220), <i>B. lactis</i> Bi-04 (ATCC SD5219)	17×10 ⁹ , 4.17×10 ⁹	Duration of antibiotic+7 days	Placebo	≥3 loose stools (5–7 Bristol Stool Scale) in 24 hours
Pirker <i>et al</i> ⁶⁰	678 (340:338)	Inpatient >18	<i>L. casei</i> Shirota (Yakult)	6.5×10 ⁹	Duration of antibiotic+3 days	Nothing	≥3 loose stools per day for ≥3 days
Plomer <i>et al</i> ⁶¹	130 (65:65)	Outpatients 18–65 being treated for <i>H. pylori</i>	<i>B. clausii</i>	6×10 ⁹	Duration of antibiotic+7 days	Placebo	Not noted
Plummer <i>et al</i> ⁶²	20 (69:69)	Inpatient >18	<i>L. acidophilus</i> , <i>B. bifidum</i>	20×10 ⁹	20 days	Placebo	Not noted
Pozzoni <i>et al</i> ⁶³	204 (106:98)	Inpatient >50	<i>S. boulardii</i>	10×10 ⁹	Duration of antibiotic+7 days	Placebo	≥3 loose stools (5–7 Bristol Stool Scale) for ≥2 days
Rajkumar <i>et al</i> ⁶⁴	1126 (549:577)	Inpatient ≥55	<i>L. casei</i> DN114001, <i>L. delbrueckii</i> subspecies bulgaricus, <i>S. thermophilus</i>	20.4×10 ⁹	Duration of antibiotic+7 days	Placebo	≥2 loose stools (5–7 Bristol Stool Scale) in 24 hours
Safdar <i>et al</i> ⁶⁵	39 (23:16)	Inpatient >18	<i>L. acidophilus</i>	60×10 ⁹	Duration of antibiotic+14 days	Placebo	≥2 consecutive days of Stool Consistency Continuum score 1, 2 or 3
Sampalis <i>et al</i> ⁶⁶	437 (216:221)	Inpatient >18	<i>L. acidophilus</i> + <i>L. casei</i> (Bio-K+CL1285, Bio-K+International, Canada)	50×10 ⁹	Duration of antibiotic+5 days	Placebo	≥1 day of ≥1 episode of loose stool
Selinger <i>et al</i> ⁶⁷	122 (61:61)	Inpatient >18	<i>B. breve</i> , <i>B. longum</i> , <i>B. infantis</i> , <i>L. acidophilus</i> , <i>L. plantarum</i> , <i>L. paracasei</i> , <i>L. delbrueckii</i> subspecies bulgaricus, <i>S. thermophilus</i> (VSL#3)	900×10 ⁹	Duration of antibiotic+7 days	Placebo	≥3 loose stools (5–7 Bristol Stool Scale) in 24 hours

Continued

Table 1 Continued

Reference	Total participants (N probiotic: N control)	Healthcare setting and age of patients	Probiotic species	Daily probiotic dose (cfu)	Duration of probiotic therapy	Control	Outcome (AAD) measurement
Shimbo <i>et al</i> ⁶⁸	35 (18:17)	Outpatients >18 being treated for <i>H. pylori</i>	<i>C. butyricum</i> MIYAIRI 588	Not noted	14 days	Nothing	Not noted
Song <i>et al</i> ⁶⁹	214 (103:111)	Inpatient >18	<i>L. rhamnosus</i> R0011+ <i>L. acidophilus</i> R0052	4×10 ⁹	14 days	Placebo	≥3 loose stools (5–7 Bristol Stool Scale) in 24 hours
Surawicz <i>et al</i> ⁷⁰	180 (116:64)	Inpatient >18	<i>S. boulardii</i>	Not noted	Duration of antibiotic+14 days	Placebo	≥3 loose or watery stools per day for ≥2 consecutive days
Thomas <i>et al</i> ⁷¹	267 (133:134)	Inpatient >18	<i>L. rhamnosus</i> GG	20×10 ⁹	14 days	Placebo	Loose stools (1–3 on Stool Consistency Continuum) for ≥2 or more consecutive days, or ≥3 more than patient's normal daily number of bowel movements
Velasco <i>et al</i> ²⁷	314 (122:125:67) (probiotic:placebo: nothing)	Inpatient >18	<i>L. acidophilus</i> La-5, <i>L. casei</i> Lc-01, <i>B. lactis</i> Bb-12 as probiotics and <i>S. thermophilus</i> STY-31, <i>L. bulgaricus</i> LBY-27 as starter strains in both yoghurt drinks	17–23×10 ⁹ plus starter strains	Duration of antibiotic+5 days	Placebo and nothing control groups	≥3 loose stools (5–7 Bristol Stool Scale) for ≥2 days
Wenus <i>et al</i> ⁷²	63 (34:29)	Inpatient >18	<i>L. rhamnosus</i> GG (LGG), <i>L. acidophilus</i> La-5 and <i>B. animalis</i> subspecies lactis BB-12	52.5×10 ⁹	Not noted	Placebo	≥3 loose stools per day for consecutive 2 days during the test period
Wong <i>et al</i> ⁷³	158 (76:82)	Inpatient >18	<i>L. casei</i> Shirota (Yakult)	6.5×10 ⁹	Duration of antibiotic+7 days	Nothing	≥3 loose stools (5–7 Bristol Stool Scale) for ≥2 days
Wright <i>et al</i> ⁷⁴	86 (41:46)	Inpatient >65	<i>L. casei</i> Shirota (Yakult)	13×10 ⁹	Duration of admission	Placebo	≥3 loose stools (5–7 Bristol Stool Scale) for ≥2 days
Wu <i>et al</i> ³¹	196 (65:67:64) (high:low:nothing)	Inpatient >18	<i>B. longum</i> , <i>L. acidophilus</i> , <i>E. faecalis</i>	48×10 ⁹ or 24×10 ⁹	14 days	Nothing	Not noted

AAD, antibiotic-associated diarrhoea.

	Sequence Generation	Allocation concealment	Blinding of participants and personnel for All outcomes	Blinding of outcome assessors for All outcomes	Incomplete outcome data for All outcomes	Selective outcome reporting	Other sources of bias
Allen 2013	+	+	+	+	+	+	+
Beausoleil 2007	?	?	+	+	+	+	+
Benival 2003	+	?	-	+	+	+	+
Bravo 2008	?	?	+	+	+	+	+
Can 2006	?	?	+	+	+	?	+
Chatterjee 2013	+	+	+	+	+	+	+
Cimpeman 2011	?	?	+	+	+	+	+
Cindruk 2007	+	?	+	+	?	+	?
De Vrese 2011	?	?	+	?	+	+	+
Duman 2005	?	?	?	?	+	-	?
Ehrhardt 2016	+	+	+	+	?	+	+
Evans 2016	+	+	+	+	+	+	+
Gao 2010	+	+	+	+	+	+	?
Gotz 1979	+	?	+	+	+	+	+
Helps 2015	+	+	+	+	+	+	+
Hickson 2007	+	?	+	+	+	-	?
Horosheva 2014	+	+	+	+	+	+	+
Iamharit 2010	?	?	+	-	+	+	+
Imase 2008	?	?	?	?	+	+	-
Khanal 2015	?	?	?	?	+	?	?
Koning 2008	?	?	+	+	+	+	?
Lewis 1998	?	?	+	+	+	+	+
Lonnermark 2010	+	+	+	+	?	+	-
McFarland 1995	?	+	+	+	-	+	-
Ouwehand 2014	+	+	+	+	+	+	-
Pirker 2013	?	?	?	?	+	?	+
Plomer 2020	+	+	+	?	+	+	+
Plummer 2004	?	?	+	+	+	+	-
Pozzoni 2012	+	+	+	+	?	+	+
Rajkumar 2020	+	+	+	+	-	-	+
Safdar 2008	?	?	+	+	+	+	?
Sampalis 2010	?	?	+	+	+	?	+
Selinger 2013	+	+	+	+	?	+	?
Shimbo 2005	?	?	?	?	?	+	?
Song 2010	?	?	+	+	+	+	+
Surawicz 1989	?	?	+	+	-	?	+
Thomas 2001	+	+	+	+	?	+	+
Velasco 2019	+	+	+	+	+	+	+
Wenus 2008	?	?	+	+	-	+	+
Wong 2013	?	?	-	-	+	+	?
Wright 2015	?	?	+	+	+	+	+
Wu 2020	+	+	?	?	+	+	+

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

comparison. One study compared its treatment group to both a placebo group and a no treatment control.²⁷ Four trials compared two probiotic arms of differing doses with a control group.²⁸⁻³¹ Where there were two treatment groups (eg, high dose and low dose) and one control group, the control group was split so that half served as comparator for each arm, in accordance with the Cochrane Systematic Review Guidelines.³² Similarly in one study³³ where a probiotic group was compared with a placebo and 'no treatment' control, the probiotic group was split. In one study²⁷ the placebo milk contained a higher concentration of starter strains than the probiotic milk. We combined the groups to make it an overall treatment group, which the authors had done themselves in the 'both' group, compared with a 'no treatment' group. Only one study was found to compare two strains of the same probiotic species; however, it was excluded as it was not randomised.³⁴

The overall pooled results of the complete case analysis of 42 studies (reporting on 11 305 participants) (figure 3), comparing probiotics with any control, favoured probiotics demonstrating a statistically significant reduction in the incidence of AAD. The pooled RR of 0.63 (RR=0.63 (95% CI 0.54 to 0.73), p<0.00001) indicates that those who took probiotics were over one-third less likely to develop AAD. These data suggest that the NNT, to prevent one case of AAD would be 20 patients. Statistically significant heterogeneity was detected for this comparison (p<0.00001; I²=60%). We used a random effects model for this analysis based on the heterogeneity of the study methodologies.

Subgroup and heterogeneity analysis

When subgroup analyses were performed, where probiotics were compared with placebo (RR=0.69 (95% CI 0.60 to 0.80), p<0.00001), and where probiotics were compared with no treatment (RR=0.35 (95% CI 0.27 to 0.47), p<0.00001), a significant reduction in relative risk of diarrhoea was noted (Forest plots available in online supplemental file 1). The difference in effect size may be explained as placebo effect.

Across all of the subgroup analyses, the I² statistic ranged from 0% to 78%. There was also substantial clinical and methodological heterogeneity, therefore we used a random effects model for all analyses. There was substantial variation in the AAD definition employed in the included studies (table 1). Although 13 studies defined AAD as ≥3 loose stools (5-7 Bristol Stool Scale) in 24 hours, 12 defined AAD as ≥3 loose stools (5-7 Bristol Stool Scale) in 2 days or more, 11 studies used various other definitions of AAD and 5 studies made no mention of their definition.

Subgroup analysis: probiotic dose

Four studies directly compared high dose and low dose of the same probiotic.²⁸⁻³¹ The higher dose group demonstrated a significant reduction in the relative risk of AAD

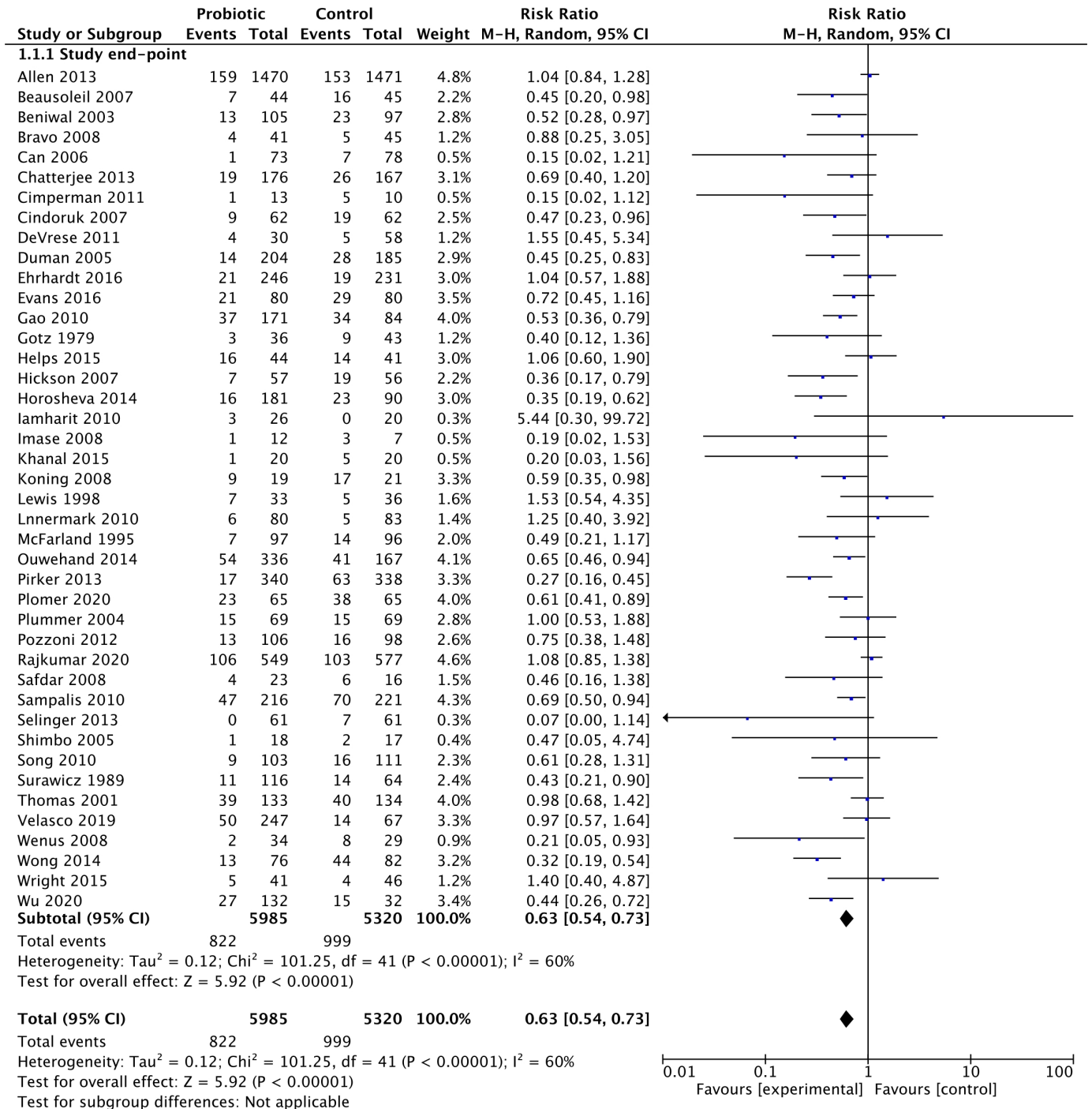


Figure 3 Forest plot of comparison. 1 probiotic versus any control, outcome: 1.1 incidence antibiotic-associated diarrhoea: complete case.

(RR 0.54 (95% CI 0.38 to 0.76), $p=0.0004$) (Forest plot available in online supplemental file 1).

Subgroup analysis: probiotic species

Most studies used probiotic formulations containing more than one probiotic species, so a subgroup analysis was performed on all individual species mentioned in included studies (table 2). Where only one study existed that used a particular strain, we analysed that study's outcome data alone. The following probiotic strains demonstrated significant reduction in AAD

when compared with a control: *L. acidophilus*, *L. bulgaricus*, *L. casei*, *L. paracasei*, *L. rhamnosus*, *Lactobacillus* spp, *S. boulardii*, *B. animalis* ssp *Lactis*, *B. longum*, *B. licheniformis*, *B. subtilis* and *Bacillus clausii*. However, *L. helveticus*, *L. plantarum*, *L. reuteri*, *B. bifidum*, *S. thermophilus* and *C. butyricum* provided no improvement in AAD compared with control.

Subgroup analysis: concurrent *H. pylori* treatment

In the seven RCTs investigating adjunct probiotic use with antibiotics for *H. pylori* treatment we found a reduction in

Table 2 Subgroup analyses by species or genus (Forest plots for all subgroup analyses available in online supplemental file 1)

Species	Studies (N)	Effect size
<i>L. acidophilus</i>	18 (6077)	RR=0.66 (95% CI 0.54 to 0.80), p<0.0001
<i>L. bulgaricus</i>	7 (1996)	RR=0.60 (95% CI 0.37 to 0.97), p=0.04
<i>L. casei</i>	11 (3382)	RR=0.59 (95% CI 0.42 to 0.83), p=0.003
<i>L. helveticus</i>	2 (239)	Not significant
<i>L. paracasei</i>	3 (665)	RR=0.60 (95% CI 0.41 to 0.88), p=0.01
<i>L. plantarum</i>	3 (325)	Not significant
<i>L. reuteri</i>	1 (23)	Not significant
<i>L. rhamnosus</i>	5 (779)	RR=0.71 (95% CI 0.52 to 0.97), p=0.03
<i>Lactobacillus</i> spp	28 (7851)	RR=0.63 (95% CI 0.52 to 0.76), p<0.00001
<i>S. boulardii</i>	9 (1827)	RR=0.63 (95% CI 0.46 to 0.86), p=0.004
<i>B. animalis</i> ssp <i>lactis</i>	6 (1351)	RR=0.70 (95% CI 0.54 to 0.91), p=0.009
<i>B. bifidum</i>	4 (3165)	Not significant
<i>B. licheniformis</i>	1 (181)	RR=0.39 (95% CI 0.19 to 0.79), p=0.009
<i>B. longum</i>	4 (366)	RR=0.46 (95% CI 0.28 to 0.73), p=0.001
<i>B. subtilis</i>	1 (271)	RR=0.35 (95% CI 0.19 to 0.62), p=0.0004
<i>S. thermophilus</i>	6 (1917)	Not significant
<i>C. butyricum</i>	1 (19)	Not significant
<i>B. clausii</i>	1 (130)	RR=0.61 (95% CI 0.41 to 0.89), p=0.01

RR, risk ratio.

diarrhoeal side effects of 45% (RR=0.55 (95% CI 0.41 to 0.73), p<0.0001) (Forest plot available in online supplemental file 1).

Sensitivity analysis: baseline risk of AAD

In a *post hoc* analysis we divided our included studies into low (0%–10%; seven studies), moderate (11%–30%; 21 studies) and high (>31%; 14 studies) baseline risk of AAD. The pooled studies with a low baseline risk of AAD did not show any difference in risk, but trials enrolling participants with a moderate or high baseline risk for developing AAD demonstrated 39% (RR=0.61 (95% CI

0.48 to 0.78), p<0.0001) and 45% (RR=0.55 (95% CI 0.46 to 0.66), p<0.00001) risk reduction, respectively (Forest plots available in online supplemental file 1).

Sensitivity analysis: high/unknown risk of bias

To examine for robustness we pooled data from the studies which we assessed as low risk of bias in all domains, and separately pooled the studies which scored high or unknown risk of bias in any domain. In our sensitivity analysis with the high and unknown risk of bias studies removed, the protective effect of probiotics against AAD was no longer statistically significant (RR=0.78 (95% CI 0.57 to 1.07), p=0.13). However, with only the high risk of bias studies removed from the complete data set, a similar pooled protective effect of probiotics was found (RR=0.65 (95% CI 0.54 to 0.78), p<0.00001) (Forest plots available in online supplemental file 1).

Adverse events

Of the 42 included studies, 32 reported on adverse events. No serious adverse events were reported in any of the included studies. One study reported four (2.0%) non-serious adverse events in the probiotic group compared with none in the control group,³⁵ and another commented that their probiotic milk was less well tolerated than their placebo milk.²⁷

Small study effects

On inspection, the funnel plot of the complete case analysis (figure 4) is symmetrical, which suggests little evidence of publication bias.

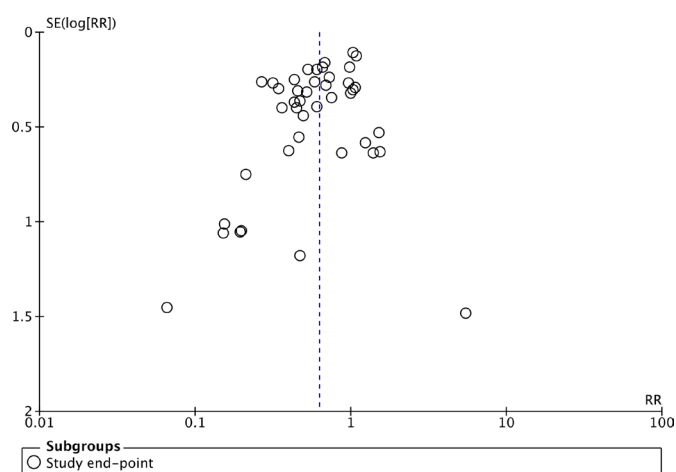


Figure 4 Funnel plot of comparison: 1 probiotic versus any control, outcome: 1.1 incidence antibiotic-associated diarrhoea: complete case. RR, risk ratio.

Overall quality of evidence

Using the GRADE approach²⁶ we rated the overall quality of the evidence as moderate. Although all included studies were RCTs, many demonstrated design limitations, mainly reflecting the reporting of sequence generation and allocation concealment in older studies, which suggests some risk of bias. This was balanced, however, by a good magnitude of effect and dose–response gradient, increasing the certainty of this body of evidence.

DISCUSSION

Summary of evidence

The principal finding of this review is that probiotics significantly reduce the risk of AAD in adults, with an NNT of 20 patients. These results were robust in subgroup analyses, with high doses more effective than lower doses, and some species more effective than others. As is the nature of systematic reviews, we found significant heterogeneity in study designs and population, severity of illness of the study group, antibiotics administered, as well as probiotic species and strains used, dose, timing and duration of probiotic administration. It may be important to note that our subgroup analysis of low baseline risk studies failed to find a statistically significant effect of probiotics. Therefore our overall effect estimate may not be directly applicable to clinical scenarios with inherent lower baseline risk of AAD. Using the GRADE criteria,²⁶ the quality of the evidence included in our meta-analysis was moderate and therefore it would be appropriate to base future clinical practice on our results.

Our results show evidence of a placebo effect, with a reduction in risk of AAD of 31% when probiotics were compared with placebo, but 65% when probiotics were compared with no treatment. Placebo effect is not well understood but this could be attributed to expectations of symptom change with neurobiological underpinnings and actual effects on the brain and body.³⁶ This effect could be investigated further in well-designed, three-armed, RCTs.

Secondary objectives included subgroup analyses of dose–response and species-specific response. In studies where dosages of the same species were compared,^{28–31} higher doses showed a significantly greater benefit (RR=0.54). It is difficult to interpret the dosage effect as the four studies that compared different doses of the same probiotic species made comparisons of differing magnitudes. Probiotic course duration was reported in most studies (40 out of 42), ranging from 5 to 56 days. Most commonly, probiotics were administered for the duration of antibiotic therapy plus a further 7 days, or a total of 14 days. It would be biologically plausible to suggest that probiotic use should be continued for some period after the cessation of antibiotics. This is another question worth investigating in future trials.

Many studies used blends of probiotic species and strains, which made it problematic to establish independent associations. In our subgroup analyses, the individual

probiotic species that demonstrated the greatest effect sizes were *B. licheniformis* (one study, RR=0.39), *B. longum* (four studies, RR=0.46) and *B. subtilis* (one study, RR=0.35). Although demonstrating a more moderate effect size, *L. acidophilus* (18 studies, RR=0.66), *L. casei* (11 studies, RR=0.59) and *S. boulardii* (nine studies, RR=0.63) were used in many more studies. Overall, the lactobacillus genus showed a good effect with a small CI. The individual species *L. acidophilus* was used in the greatest number of studies, demonstrating a moderate effect with a relatively small CI. Moderate effect sizes were noted with other species and strains, which may be worth looking into more specifically in future trials. *L. helveticus*, *L. plantarum*, *L. reuteri*, *B. bifidum*, *S. thermophilus* and *C. butyricum* did not show evidence of effectiveness in reducing incidence of AAD.

We found only one study³⁴ comparing two strains of the same probiotic species, *L. casei* DN-114001, (Actimel) and *L. casei* Shirota (Yakult). In this study *L. casei* DN-114001 was significantly more effective for preventing AAD than *L. casei* Shirota. However, we were unable to include these data in our review as it was not randomised. Future RCTs should focus on direct comparisons of single or combined probiotic species and strains.

The most commonly identified indication for antibiotics was treatment of *H. pylori*. The reduction in diarrhoeal side effects by 45%, through the use of adjunct probiotics, may be a significant finding in improving quality of life for these patients.

Limitations

A limitation of this study is that the only outcome measured was incidence of diarrhoea. This review's utility in clinical practice may have been improved by also analysing duration of AAD, diarrhoea severity, need for hospitalisation due to diarrhoea and quality of life measures. Additionally, it may have been informative to correlate outcomes with the duration of probiotic course or the date of probiotic initiation in relation to antibiotics.

Subgroup analysis by antibiotic would have been informative but was not possible as many of the included studies did not state the antibiotic name, class, route of administration, dose or course length that participants were administered. Future studies could focus on this.

This study was somewhat limited in scope as we only included studies published in English. Additionally, the initial search was a title search as opposed to keyword search, which may explain the lower number of studies initially identified, compared with the recent Cochrane review.²¹

Agreements and disagreements with other studies

This study is concordant with findings from the aforementioned Cochrane systematic review.²¹ Goldenberg found that probiotics led to a significant reduction in incidence of AAD from 18% to 12% of participants (RR=0.58, 95% CI 0.48 to 0.70). The present review included 18 additional studies (4487 additional participants). This



increase in total population increases the power of our review to detect smaller clinically relevant differences between groups in incidence of AAD.

Our subgroup analyses found similarly to one previous meta-analysis³⁷ that the *Lactobacillus* and *Saccharomyces* genera reduced incidence of AAD. A more recent meta-analysis³⁸ found, also concordantly, that many *Lactobacillus* and *Bifidobacteria* species and *S. boulardii* were effective. Previous meta-analyses have not reported on dose–response.

Our subgroup analyses were also in agreement with The American Gastroenterological Association Clinical Practice Guidelines on the Role of Probiotics in the Management of Gastrointestinal Disorders³⁹ which suggest the use of *S. boulardii*; or the two-strain combination of *L. acidophilus* CL1285 and *L. casei* LBC80R among other probiotic species for prevention of AAD.

Contrary to the findings of our review, one meta-analysis⁴⁰ reported that probiotics may not be effective in reducing the incidence of AAD. However, only 13 studies were analysed, including adults over 65 only. This suggests a need for looking separately at the effectiveness of probiotics in populations of younger and older adults.

CONCLUSIONS

This review found evidence supporting a moderate protective effect for probiotics in preventing AAD. In absolute terms, the NNT, to prevent one case of AAD would be 20 patients. These results should be applied with caution in clinical scenarios with inherent lower baseline risk of AAD. In studies that compared dosage of the same probiotic, higher doses were found to be significantly more effective, suggesting a recommended dose of greater than 10 billion cfu per day. Although the probiotic species that demonstrated the greatest effect were *B. licheniformis*, *B. longum* and *B. subtilis*, each was studied in only a handful of trials. The species *L. acidophilus*, *L. casei* and *S. boulardii*, still demonstrating moderate effect sizes in preventing AAD, were used in many more trials. A good effect size was found supporting the use of probiotics, given concurrently with antibiotics for *H. pylori* eradication therapy.

This review has demonstrated overall effectiveness of probiotics for the prevention of AAD, including a dose–response and some species-specific effectiveness of probiotics. Further high-quality trials are needed, focusing on direct comparison of doses, comparison of individual species and combinations of species. Future studies should record not only incidence of diarrhoea, but also duration, severity, quality of life measures and length of stay in hospital so that an assessment of the cost–benefit of probiotic therapy can be made. Future trials should ensure there is adequate blinding and reporting of adverse events.

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