Probiotics for the Prevention and Treatment of Antibiotic-Associated Diarrhea

A Systematic Review and Meta-analysis

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Context Probiotics are live microorganisms intended to confer a health benefit when consumed. One condition for which probiotics have been advocated is the diarrhea that is a common adverse effect of antibiotic use.

Objective To evaluate the evidence for probiotic use in the prevention and treatment of antibiotic-associated diarrhea (AAD).

Data Sources Twelve electronic databases were searched (DARE, Cochrane Library of Systematic Reviews, CENTRAL, PubMed, EMBASE, CINAHL, AMED, MANTIS, TOXLINE, ToxFILE, NTIS, and AGRICOLA) and references of included studies and reviews were screened from database inception to February 2012, without language restriction.

Study Selection Two independent reviewers identified parallel randomized controlled trials (RCTs) of probiotics (*Lactobacillus, Bifidobacterium, Saccharomyces, Streptococcus, Enterococcus*, and/or *Bacillus*) for the prevention or treatment of AAD.

Data Extraction Two independent reviewers extracted the data and assessed trial quality.

Results A total of 82 RCTs met inclusion criteria. The majority used *Lactobacillus*-based interventions alone or in combination with other genera; strains were poorly documented. The pooled relative risk in a DerSimonian-Laird random-effects meta-analysis of 63 RCTs, which included 11 811 participants, indicated a statistically significant association of probiotic administration with reduction in AAD (relative risk, 0.58; 95% CI, 0.50 to 0.68; $P < .001$; I^2, 54%; [risk difference, –0.07; 95% CI, –0.10 to –0.05], [number needed to treat, 13; 95% CI, 10.3 to 19.1]) in trials reporting on the number of patients with AAD. This result was relatively insensitive to numerous subgroup analyses. However, there exists significant heterogeneity in pooled results and the evidence is insufficient to determine whether this association varies systematically by population, antibiotic characteristic, or probiotic preparation.

Conclusions The pooled evidence suggests that probiotics are associated with a reduction in AAD. More research is needed to determine which probiotics are associated with the greatest efficacy and for which patients receiving which specific antibiotics.

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THE USE OF ANTIBIOTICS THAT DISturb the gastrointestinal flora is associated with clinical symptoms such as diarrhea, which occurs in as many as 30% of patients.[1,2] Symptoms range from mild and self-limiting to severe, particularly in *Clostridium difficile* infections, and antibiotic-associated diarrhea (AAD) is an important reason for nonadherence with antibiotic treatment.[3]

Probiotics are microorganisms intended to have a health benefit when consumed. Synbiotics refer to preparations in which probiotic organisms and prebiotics (nondigestible food ingredients that may benefit the host by selectively stimulating bacteria in the colon) are combined.

Potentially, probiotics maintain or restore gut microecology during or after antibiotic treatment through receptor competition, competition for nutrients, inhibition of epithelial and mucosal adherence of pathogens, introduction of lower colonic pH favoring the growth of nonpathogenic species, stimulation of immunity, or production of antimicrobial substances.[4,5]

There is an increasing interest in probiotic interventions, and evidence for

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the effectiveness of probiotics in preventing or treating AAD is also increasing.[6,7] Previous reviews have been nonsystematic, have focused on specific patient populations or probiotic genera, and have not included the latest clinical trials.[1,8] A 2006 meta-analysis[9] on probiotic use for AAD included 25 RCTs and a 2006 review[10] included 16 relevant RCTs. Both studies suggested that probiotic use was associated with reduced risk of AAD. Yet, more than 30 additional RCTs on the topic have been published in the international literature since. A recent Cochrane review on pediatric AAD suggested a protective association of probiotic use in preventing AAD in children. Most studies of probiotics include adult participants, which suggests the evidence in adult AAD prevention should also be revisited.[11]

The objective of this systematic review and meta-analysis is to evaluate broadly the available evidence on probiotics and synbiotic interventions including the genera *Lactobacillus*, *Bifidobacterium*, *Saccharomyces*, *Streptococcus*, *Enterococcus*, and *Bacillus*, alone or in combination, for the prevention or treatment of AAD.

METHODS

The review protocol has been registered in PROSPERO International Prospective Register of Systematic Reviews (crd.york.ac.uk/prospero/index.asp Identifier: CRD42011001296).

Study Selection

Parallel RCTs that compared probiotic use as adjunct antibiotic treatment with a concurrent control group receiving no treatment, placebo, or a different probiotic or probiotic dose were eligible for inclusion in the review. Participants of all ages treated with antibiotics, regardless of the indication and the patients' underlying symptomatology, were included. Interventions based on the genera *Lactobacillus, Bifidobacterium, Saccharomyces, Streptococcus, Enterococcus*, and/or *Bacillus* alone or in combination, using live (active or lyophilized) microorganisms in probiotic or synbiotic preparations, were eligible. RCTs of prevention as well as treatment of AAD were included. Trials were also included if probiotics were given alongside antibiotics to enhance treatment effects (eg, *Helicobacter pylori* eradication), rather than to prevent adverse effects of antibiotics, if the outcome of diarrhea was reported. All reports of diarrhea were considered (as main treatment effects, reasons for dropouts, or adverse effects). This analysis used the original study's definition of diarrhea, which ranged from uncomplicated diarrhea to severe diarrhea with complications such as electrolyte imbalance, and included outcomes such as watery stool, stool consistency, self-reported diarrhea, and physician-defined diarrhea.

Literature Search

As part of a larger project on the safety of probiotic use,[6] we searched 12 electronic databases (DARE, Cochrane Library of Systematic Reviews, CENTRAL, PubMed, EMBASE, CINAHL, AMED, MANTIS, TOXLINE, ToxFILE, NTIS, AGRICOLA), from database inception to February 2012 without language restriction, to identify probiotics publications. The search was broad and not restricted to individual genera used as probiotics or to any clinical indications or outcomes; the exact search terms for PubMed are shown in eFigure 1 (available at http://www.jama.com). In addition, we searched clinicaltrials.gov, screened references of included studies and reviews, and handsearched the *International Journal of Probiotics and Prebiotics*.

Study Selection

Two reviewers independently assessed publications for inclusion in the review. Discrepancies were resolved through discussion by the review team.

Data Abstraction

Two independent reviewers extracted trial details pertaining to the participants, antibiotics and probiotics interventions and comparators, and results regarding diarrhea, using a standardized form. Discrepancies were resolved through discussion. The primary outcome was the number of participants with diarrhea in each treatment group. We also extracted other relevant outcomes such as the severity of diarrhea or measures of stool consistency. We extracted probiotics-related adverse effects such as infections because of the administered organism. When more than 1 active treatment group was investigated, we selected the group first mentioned as the main treatment group.

Quality Assessment

We applied the Cochrane Risk of Bias tool to assess sequence generation; allocation concealment; participant, personnel, and outcome assessor blinding; attrition bias; incomplete outcome data; selective outcome reporting; and other sources of bias.[12] In addition, we assessed the reporting and ascertainment of included strains, the statistical power, and the funding and potential for conflict of interest associated with individual trials.

Data Synthesis

We combined trials in a random-effects meta-analysis calculating the relative risk (RR) and the 95% CI in trials reporting the number of patients with diarrhea, using the DerSimonian-Laird algorithm in The Metafor Package—a meta-analysis package for R.[13,14] In addition, we computed the risk difference (RD) and the number needed to treat (NNT) for the number of participants with AAD based on an analysis using RD. Other study characteristics and results were summarized narratively.

Sensitivity and Subgroup Analyses

Subgroup analyses were based on the probiotic genus, participants' age, clinical condition, and setting. To investigate whether any observed differences between subgroups were statistically significant, meta-regressions were undertaken to

compare the ratio of relative risks (RRR) using the presence of the subgroup-defining variable as a moderator. To assess heterogeneity, we computed the I^2 statistic. We explored potential sources of heterogeneity and the robustness of results further for the aim of the study, study quality, the comparator, antibiotic treatment duration, and publication year. Potential for publication bias was assessed with Egger regression and the Begg rank test.[15,16]

RESULTS

The search for publications on probiotic use identified 15 214 titles and abstracts, of which 2426 were obtained as full-text publications and screened for inclusion in the review. A total of 82 RCTs met inclusion criteria. Details of the study flow are documented in eFigure 2. The citations and the characteristics of all RCTs meeting inclusion criteria for the review are documented in detail in the eTable. The included RCTs primarily enrolled adults for studies in which age was described (52/82 RCTs). The clinical indication for antibiotics varied; the most common reason was *H pylori* eradication (24/82), but studies with this indication still comprised a minority of the studies. Sixteen trials reported the use of single antibiotics such as amoxicillin, azithromycin, and clarithromycin, while others included numerous antibiotics or were otherwise unspecified. Two trials were identified that explicitly investigated probiotics for the treatment, rather than the prevention or potential treatment of AAD, with all participants experiencing AAD at study commencement.

Most RCTs randomized a moderate number of participants (median, 93.5; mean [SD], 161.3 [192.3]) to either adjunctive probiotics treatment or placebo (56/82), no treatment (ie, antibiotics only, 23/82), heat-killed organisms matching the probiotics (3/82), or standard treatment (diosmectite, 1/82). The probiotic interventions were primarily *Lactobacillus* based, either alone or combined with other genera, (57/82), eg, *Bifidobacterium* (32/82). Sixteen studies used an exclusively yeast-based intervention (*Saccharomyces boulardii* [*cerevisiae*] or *Hansen* CBS 5926). Few studies used *Enterococcus*, *Streptococcus,* or *Bacillus* strains.

Table 1. Quality Criteria and Risk of Bias

	No. (%)[a]		
	High Quality Low Risk of Bias	Low Quality High Risk of Bias	Unclear Quality Unclear Risk of Bias
Included strains determined	2 (2)	41 (50)	39 (48)
Power calculation for antibiotic-associated diarrhea	25 (30)	39 (48)	18 (22)
No conflict of interest, funding declared	13 (16)	17 (21)	52 (63)
Risk of bias assessments[b]			
Sequence generation	26 (32)	5 (6)	51 (62)
Allocation concealment	18 (22)	0	64 (78)
Blinding	53 (65)	15 (18)	14 (17)
Free of attrition bias	38 (46)	31 (38)	13 (16)
Free of selective outcome reporting	59 (72)	14 (17)	9 (11)
Other sources of bias	50 (61)	4 (5)	28 (34)

[a] No. (%) is based on 82 randomized controlled trials that met inclusion criteria.
[b] Assessments made using the Cochrane Risk of Bias Tool (version 2009).

The quality of the reporting was low; 59 trials lacked adequate information to assess the overall risk of bias. Results of the quality assessment for individual features are shown in TABLE 1. Half the RCTs reported only the genus and species that were used in the intervention but not the strain (41/82), and many did not state that treatment allocation was concealed (64/82), or did not report an intention-to-treat analysis (31/82). Nearly half did not report a power calculation (39/82). However, 53 of the 82 trials reported that participants and outcome assessors were blind to the intervention. Seventeen trials were classified as industry sponsored; 52 did not clarify the role of funding, questions about conflict of interest remained, or both; and 13 trials explicitly stated no competing interest.

Details of included double-blind placebo-controlled trials aiming to reduce or treat AAD and reporting the number of participants with AAD in both treatment groups are shown in TABLE 2 and TABLE 3.[17-51]

Efficacy

Of all included trials, 63 reported the number of participants with diarrhea and the number of participants randomized to both treatment groups.[17-78] The RR (95% CI) results of each trial are shown in the FIGURE[17-78]; most trials did not show a statistically significant advantage of probiotic use. However, across 63 RCTs (N = 11 811 participants), probiotic use was associated with a lower RR of developing diarrhea compared with a control group not using probiotics, (pooled RR, 0.58; 95% CI, 0.50 to 0.68; $P < .001$; I^2, 54%). To test the robustness of this result, we omitted each trial, in turn, from the analyses; the pooled result remained statistically significant at $P < .001$ for all 63 analyses. The pooled RD of developing AAD was –0.07 (95% CI, –0.10 to –0.05; $P < .001$); the NNT was 13 (95% CI, 10.3 to 19.1). There was no evidence of publication bias (Egger regression test $P = .26$; Begg rank test $P = .34$).

Most studies (62/82) explicitly administered probiotics to prevent or treat AAD. However, all trials that reported the outcome of interest and described an intervention in which antibiotics and probiotics were given simultaneously were included (eg, to

Table 2. RCTs of AAD Treatment or Prevention With Probiotics: Genera Blends or Saccharomyces Only[a]

Source	Condition	Antibiotic, Dose, and Duration[b]	Probiotics Genus, Strain, Potency, Dose, and Duration[b]	Diarrhea Definition and Report Type
		Genera Blends		
Bhalla,[38] 2011	Requiring antibiotics for 7 d	Systemic oral antibiotics for 7 d	*Lactobacillus acidophilus*, LA-5; and *Bifidobacterium*, BB-12 1 techsule, 2×/d for 14 d	Reported by diary card
Corrêa et al,[18] 2005	Receiving antibiotics	NA	*Bifidobacterium lactis*, 10^7 CFU; and *Streptococcus thermophilus*, 10^6 CFU ≥500 mL as needed for 15 d	≥3 Liquid stools/d for ≥2 consecutive d; staff recorded
Hickson et al,[19] 2007	Respiratory infections, orthopedic surgery, other	NA	*Lactobacillus casei*, DN-114001, 10^8 CFU/mL (mean 2.2×10^8 in tests); *S thermophilus*, 10^8 CFU/mL; and *Lactobacillus bulgaricus*, 10^7 CFU/mL 97 mL, 2×/d, duration varied	≥2 Stools/d for ≥3 d; staff reported
Jirapinyo et al,[20] 2002	Sepsis or meningitis	NA	*L acidophilus*; and *Bifidobacterium infantis* 1 capsule, 3×/d for 7 d	NA
Myllyluoma et al,[21] 2005	*Helicobacter pylori*	Clarithromycin 500 mg, 2×/d; and amoxicillin 1 g, 2×/d for 7 d	*Lactobacillus rhamnosus*, GG, 6×10^8 CFU/mL (2 *Lactobacillus* strains combined; microbial quality assessed regularly); *L rhamnosus*, LC; and *Bifidobacterium breve*, Bb99, 7×10^6 CFU/mL 65 mL, 2×/d for 7 d, then 65 mL, 1×/d for 3 w	≥3 Watery or loose stools/d for ≥2 consecutive d; self reported, De Boer modified
Plummer et al,[22] 2004	NA	NA	*L acidophilus*, 2×10^{10} CFU (2 strains combined); and *Bifidobacterium bifidum* 1 capsule/d for 20 d	NA; staff recorded
Selinger et al,[23] 2011	Hospitalized on systemic antibiotics	Systemic antibiotics dose and duration varied	*Lactobacillus*; *Bifidobacterium*; and *Streptococcus* 1 sachet, 2×/d for length of antibiotic use	NA
Stein et al,[24] 2007	NA	NA	*L acidophilus*, 1.5×10^9 CFU; *B bifidum*, 1.5×10^9 CFU; *L bulgaricus*, 1.5×10^9 CFU; and *S thermophilus*, 1.5×10^9 CFU 1 capsule, 3×/d	≥2 Watery stools within 24 h; assessor NA
Szymański et al,[25] 2008	Acute otitis media, respiratory tract infection, urinary tract infection	NA	*Bifidobacterium longum*, PL03, 10^8 CFU (all strains combined); *L rhamnosus*, KL53A; and *Lactobacillus plantarum*, PL02 10^8 CFU, 2×/d	≥3 Loose or watery stools/d for ≥2 d; self reported
		***Saccaromyces* Only**		
Adam et al,[26] 1977	Bronchopulmonary or otorhinolaryngology infections	Penicillin; ampicillin; amoxicillin; other semisynthetics; cephalosporin; tetracycline and chloral hydrates; tetracycline derivatives dose and duration varied	*Saccharomyces boulardii* 4 capsules/d	Stool index (number of stools, consistency, color, and before/after comparison); assessor NA
Bravo et al,[27] 2008	Acute infections	Amoxicillin for 5-10 d	*S boulardii*, 5.1×10^9 CFU/capsule 1 capsule, 2×/d for 12 d	3 Loose stools on ≥2 consecutive d; self reported
Can et al,[28] 2006	Chemotherapy but not intensive care unit	NA	*S boulardii* 2×/d	NA; self reported
Cindoruk et al,[29] 2007	*H pylori*	Clarithromycin 500 mg, 2×/d; and amoxicillin 1000, 2×/d for 14 d	*S boulardii* 500 mg, 2×/d for 2 w	De Boer questionnaire, self reported
Kotowska et al,[30] 2005	Otitis media, respiratory tract infections, or both	NA	*S boulardii* 250 mg, 2×/d	≥3 Loose or watery stools/d ≥48 h; self reported
Lewis et al,[31] 1998	NA	NA	*S boulardii* 113 mg, 2×/d	≥3 Loose stools within 24 h; staff reported
McFarland et al,[32] 1995	NA	Beta-lactams	*S boulardii*, 3×10^{10} CFU/g 500 mg, 2×/d	≥3 Loose stools/d ≥2 consecutive d associated with ≥1 b-lactam with no other etiology of diarrhea; self reported
Monteiro et al,[33] 1981	Infections	Tetracycline; and betalactamines	*S boulardii* 1 capsule, 4×/d for 6 d	>2 Defecations ≥3×/d; NA
Surawicz et al,[34] 1989	NA	NA	*S boulardii, 250 mg (0.5 g lyophilized)* 2×/d	≥3 Loose or watery stools/d for ≥2 d; staff and self reported

Abbreviations: AAD, antibiotic-associated diarrhea; CFU, colony forming unit; NA, not available or not applicable.

[a] For each study, the number of patients with ADD and the number of patients overall in both the intervention and control groups, see the Figure. For further information on these studies and details of the remaining included studies see eMaterial.

[b] Indication of the antibiotics used in each study and the respective dose and duration are shown only if available. For probiotics used, the respective strain, potency, dose, and duration data are shown only if available.

enhance effectiveness of *H pylori* eradication), regardless of the study objective. When the meta-analysis was restricted to the trials explicitly aiming to prevent or treat AAD (52 RCTs), results were similar (RR, 0.58; 95% CI, 0.49 to 0.68; $P<.001$; I^2, 55%; NNT, 12). Approximately half of the trials (43 RCTs) reported a definition of the diarrhea outcome. Favorable results for probiotics were also shown in these selected trials (RR, 0.56; 95% CI, 0.47 to 0.68; $P<.001$; I^2, 57%; NNT, 10).

This analysis also investigated whether studies with a lower risk of bias reported outcomes associated with probiotics supplementation. Trial quality was generally low; however, the substantial number of double-blind RCTs (N=44) showed a statistically significant combined RR of 0.61 (95% CI, 0.52 to 0.73; $P<.001$; I^2, 50%; NNT, 14). These associations were sustained in the small number of trials that reported allocation concealment as well as double-blinding (12 RCTs [RR, 0.62; 95% CI, 0.41 to 0.95; $P=.029$; I^2, 76%; NNT, 14]). A meta-regression showed that associations regarding treatment benefits for nonblinded trials were not significantly larger (RRR, 1.24; $P=.25$). The beneficial association of probiotic use was also shown in 12 RCTs that declared the funding source and claimed to be free of conflict of interest (RR, 0.63; 95% CI, 0.42 to 0.92; $P=.018$; I^2, 68%; NNT, 15). There was no statistically significant difference in results between studies with conflict of interest compared with other studies (RRR, 1.14; $P=.49$).

Probiotic Intervention Characteristics

Many trials used blends of various probiotic genera, primarily *Lactobacillus*, alone or in combination with other probiotics. The exclusively *Lactobacillus*-based interventions (17 RCTs) reporting on the number of participants with AAD showed a pooled RR of 0.64 (95% CI, 0.47 to 0.86; $P=.004$; I^2, 56%; NNT, 14). The exclusively yeast-based interventions (15 RCTs, *Saccharomyces*) showed a pooled RR of 0.48 (95% CI, 0.35 to 0.65; $P<.001$; I^2, 56%; NNT, 10). The pooled result for 3 older studies using *Enterococcus* [*Streptococcus*] *faecium* SF68 was 0.51 (95% CI, 0.38 to 0.68; $P<.001$; I^2, 0%; NNT, 12). Subgroup analyses did not explain a substantial amount of heterogeneity across studies. Heterogeneity remained evident when analyses were restricted to individual genera. The results of the subgroups of distinct genera did not have statistically significant difference (Q (5)=4.7; $P=.45$). The identified studies that provided head-to-head comparisons of different probiotics showed no clear signal. Comparing *Lactobacillus LGG*, *Saccharomyces boulardii,* and *Lactobacillus acidophilus* plus *Bifidobacterium lactis,* one study concluded that none of the species or combinations showed substantial superiority over the others.[79] A study using 6 different probiotic preparations (*S boulardii*, *Enterococcus SF68*, *Lactobacillus LGG*, 3 different *Lactobacillus* strains, a combination of *Bifidobacterium* and *Lactobacillus* strains, or a mixture of different lactic acid bacteria) reported no difference in intestinal concerns.[80]

Subgroup analyses for each of the 6 investigated genera analyzed as ingredients of the probiotics interventions (including blends) showed statistically significant associations with the number of patients with AAD compared with control participants for all genera. Indirect comparisons across studies comparing the risk ratios of trials with and without each genus found no difference between studies associated with the genus ([*Bacillus*; RRR, 0.62; $P=.18$], [*Bifidobacterium*; RRR, 1.18; $P=.16$], [*Enterococcus*; RRR, 1.03; $P=.92$], [*Lactobacillus*; RRR, 1.14; $P=.09$], [*Saccharomyces*; RRR, 0.79; $P=.18$], and [*Streptococcus*; RRR, 1.05; $P=.82$]). The number of trials by genus ranged from 40 (*Lactobacillus*) to 3 (*Bacillus*). Most interventions were blends of probiotics, which did not allow us to establish an independent association for each genus.

Forty-five placebo-controlled trials (excluding no adjunct treatment trials) also showed a statistically significantly lower RR of AAD for participants using probiotics (RR, 0.59; 95% CI, 0.50 to 0.70; $P<.001$; I^2, 48%; NNT, 13).

Participants, Setting, and Antibiotic Characteristics

We distinguished 3 subgroups based on participant age: children (0-17 years), adults (18-65 years), and elderly adults (>65 years). A large number of studies included participants from 2 or more age groups. In the 16 RCTs that targeted children specifically, the association of probiotics with risk for AAD was 0.55 (95% CI, 0.38 to 0.80; $P=.002$; I^2, 68%; NNT, 11). In the 14 RCTs that included only participants aged 18 to 65 years, the association was an RR of 0.54 (95% CI, 0.34 to 0.85; $P=.008$; I^2, 45%; NNT, 13). Only 3 studies were identified exclusively in elderly adults that reported the number of participants with AAD. The pooled result for these trials was an RR of 0.81 (95% CI, 0.40 to 1.63; $P=.55$; I^2, 65%; NNT, 25). A meta-regression did not indicate statistically significant differences in associations between age groups, whether comparing all 3 age groups (Q (2)=0.95; $P=.62$), or only RCTs in children and adults, exclusively (Q (1)=0.01; $P=.93$).

The majority of RCTs enrolled outpatients, but 24 RCTs included hospitalized patients. In 20 RCTs, adjunct probiotics treatment was associated with a statistically significant benefit on the number of participants with AAD (RR, 0.55; 96% CI, 0.42 to 0.72; $P<.001$; I^2, 47%; NNT, 10). The indications for antibiotic use varied across participants in the included studies. The most common indication for antibiotic use in

Table 3. RCTs of AAD Treatment or Prevention With Probiotics: *Enterococcus* Only, *Lactobacillus* Only, or *Bacillus* Only[a]

Source	Condition	Antibiotic, Dose, and Duration[b]	Probiotics Genus, Strain, Potency, Dose, and Duration[b]	Diarrhea Definition and Report Type
		***Enterococcus* Only**		
Frigerio,[35] 1986	NA	NA	*Enterococcus faecium*, SF 68 2 capsules/d for 7 d	NA
Wunderlich et al,[36] 1989	Acute diarrhea while on antibiotics	NA	*E faecium*, SF 68, 7.5×10^7 CFU/capsule 1 capsule 2×/d for 7 d	≥2 Liquid or semiliquid stools/d; self reported
		***Lactobacillus* Only**		
Arvola et al,[37] 1999	Acute respiratory infections	NA	*Lactobacillus rhamnosus*, GG, 2×10^{10} CFU/capsule 1 capsule 2×/d for 7-10 d	≥3 Loose stools within 24 h for ≥2 consecutive d; parent reported
Beausoleil et al,[17] 2007	Infections needing antibiotics	NA	*Lactobacillus acidophilus*, CL1285, $\geq 5 \times 10^{10}$ CFU (both strains); and *Lactobacillus casei* 49 g/d for first 2 d, 98 g/d for length of antibiotic use	≥3 Liquid stools/d; medical record
Cimperman et al,[39] 2011	Hospitalized, most common diagnosis pneumonia	Azithromycin; cefriaxone; moxifloxacin; vancomycin; zosyn; clindamycin; meropenum; cefuroxime; amplicillin/sulbactam; and cefriaxone dose and duration varied	*Lactobacillus reuteri*, ATCC 55730, 10^8 CFU/tablet 1 tablet 2×/d for 28 d	≥3 Bowel movements/d for 2 consecutive d, fluffy pieces with ragged edges and a mushy stool or watery and no solid pieces; self reported, Bristol stool scale
Gao et al,[41] 2010	Infection	NA	*L acidophilus*, CL1285, 5×10^{10} CFU (both strains combined/capsule); and *L casei*, LBC80R 1 capsule for 5 d after last antibiotic dose 2×/d	≥3 Liquid stools/d after antibiotic with no other obvious reason for diarrhea; Bristol stool form scale per nurse, clinician, or self reported
Gotz et al[42] 1979	NA	Ampicillin 20 doses	*L acidophilus*; and *Lactobacillus bulgaricus*, 10^8 CFU/packet 1 packet 4×/d for 5 d	≥3 Bowel movements more than the patients normal daily number; staff reported
Lönnermark et al,[44] 2010	Infection	NA	*Lactobacillus plantarum*, 5×10^7 CFU/mL 200 mL/d	≥3 Loose or watery stools/d ≥2 consecutive d; self reported
Ruszczynski et al,[45] 2008	Common infections	NA	*L rhamnosus*, Pen, 2×10^9 CFU (all strains combined); *L rhamnosus*, E/N; and *L rhamnosus*, Oxy 2×10^9 CFU, 2×/d for length of antibiotic use	≥3 Lose or watery stools/d for ≥48 h and caused by *Clostridium difficile* or unexplained diarrhea; self reported

(continued)

the identified studies was *H pylori* treatment. In these 15 RCTs, adjunct probiotic use was associated with benefit (RR, 0.55; 95% CI, 0.35 to 0.86; $P=.009$; I^2, 65%; NNT, 17). The beneficial association of probiotic use was also demonstrated in the remaining 48 RCTs (RR, 0.58; 95% CI, 0.49 to 0.69; $P<.001$; I^2, 56%; NNT, 12), and the 2 subgroups were not significantly different (RRR, 1.01; $P=.96$). For trials in which a treatment schedule was reported, antibiotics were administered between 1 and 14 days, with 22 of 82 trials specifying a 7-day treatment schedule; however, neither a dichotomous analysis for the 1-week cutoff, nor a continuous-variable meta-regression for treatment duration influenced the result (dichotomized duration RRR, 0.85; $P=.61$; continuous duration RRR/d, 1.00; $P=.95$). Included studies were published over a period of more than 30 years. Newer studies may have chosen antibiotics with a better safety record. However a meta-regression did not indicate that the ratio of AAD incidences in the treatment and control groups was significantly affected by publication year (RRR/y, 1.02; $P=.07$).

Other Results

Most trials either did not specify the follow-up period, or the assessment was explicitly limited to the time of antibiotics treatment. Trials that reported AAD incidence after cessation of antibiotic therapy (7 RCTs) indicated that the number of participants experiencing AAD was lower in the probiotics groups than in control groups (RR, 0.44; 95% CI, 0.20 to 0.99; $P=.047$; I^2, 0%; NNT, 75).

In 31 RCTs, it was specified which AAD incidences required treatment, were classified by the authors as severe, led to participants stopping the antibiotics and probiotics treatment, or involved patients testing positive for *C difficile*. Adjunct probiotics treatment was associated with reductions in the number of participants experiencing severe occurrences in the studies that reported the presence or absence of these events (RR, 0.52; 95% CI, 0.36 to 0.75; $P<.001$; I^2, 0%; NNT, 69). In 14 RCTs, the pooled RR for preventing *C difficile* diarrhea was 0.29 (95% CI, 0.17 to 0.48; $P<.001$; I^2, 0%; NNT, 25), but several studies cautioned that adherence for testing was low or the number of tested samples per group was not reported.

Of the 82 trials, 4 publications reported the absence of infections and se-

Table 3. RCTs of AAD Treatment or Prevention With Probiotics: *Enterococcus* Only, *Lactobacillus* Only, or *Bacillus* Only[a] (continued)

Source	Condition	Antibiotic, Dose, and Duration[b]	Probiotics Genus, Strain, Potency, Dose, and Duration[b]	Diarrhea Definition and Report Type
		***Lactobacillus* Only**		
Safdar et al,[46] 2008	Infection	NA	*L acidophilus*, 2 × 10^{10} CFU/capsule 1 capsule 3×/d for 14 d	Bowel movement consistency on the Stool Consistency Continuum listed as 1, 2, or 3 for ≥2 consecutive d; research team and self reported (after discharge)
Sampalis et al,[40] 2010	Respiratory, skin, urogenital tract or other infections	Beta-lactams; quinolones; macrolides; clindamycin; metronidazole; septra; tetracycline; tobramycine; vancomycin; or linezolide; for a minimum of 3 d, maximum 14 d	*L acidophilus*, CL1285, 5 × 10^{10} CFU (both strains combined/3.5 oz bottle); and *L casei* 49 g/d for first 2 d, 98 g/d for 27-38 d	≥1 Unformed stools/d; self reported
Song et al,[47] 2010	Respiratory tract infection	Cephalosporins; macrolides; fluoroquinolones; antituberculosis drugs; clindamycin; penecillin; aminoglycosides; metronidazole; sulfamethoxazole/trimethoprim; and glycopeptides dose and duration varied	*L rhamnosus*, R0011, 2 × 10^{9} CFU (both strains); and *L acidophilus*, R0052 1 capsule 2×/d for 14 d	Loose, watery stool >3/d for 2 consecutive d; >2 loose stools for 2 d
Szajewska et al,[48] 2009	*Helicobacter pylori*	Amoxicillin 25 mg/kg 2×/d; and clarithromycin 10 mg/kg, 2×/d for 7 d	*L rhamnosus*, GG, 10^{9} CFU 10^{9} CFU 2×/d for 7 d	≥3 Loose or watery stools/d for ≥2 d; self reported
Tankanow et al,[40] 1990	Disease requiring amoxicillin	Amoxicillin dose and duration varied	*L acidophilus*; and *L bulgaricus* 5 × 10^{8} CFU/packet 1 packet 4×/d for 10 d	≥1 Abnormally loose bowel movermentsd; parent reported
Thomas et al,[49] 2001	Infection	NA	*L rhamnosus*, GG, 10^{10} CFU/capsule (viability tested in sample) 1 capsule 2×/d for 14 d	Watery or liquid stools (1, 2, 3 on Stool Consistency Continuum) for ≥2 consecutive d or ≥3 stools >patient's normal amount; self reported
Vanderhoof et al,[50] 1999	Acute infectious disease	NA	*L rhamnosus*, GG, 10^{10} CFU/capsule 1-2 capsules/d for 10 d	≥2 Liquid stools/d on ≥2 d; primary caregiver reported
		***Bacillus* Only**		
La Rosa,[43] 2003	Active infections	NA	*Bacillus coagulans* [*Lactobacillus sporogenes*], 5.5×10^{8} CFU/capsule 1 capsule/d for 10 d	Scale ranging from normal (0) to liquid (2); self reported

Abbreviations: AAD, antibiotic-associated diarrhea; CFU, colony forming unit; NA, not available or not applicable.
[a] For each study, the number of patients with ADD and the number of patients overall in both the intervention and control groups, see the Figure. For further information on these studies and details of the remaining included studies see eMaterial.
[b] Indication of the antibiotics used in each study and the respective dose and duration are shown only if available. For probiotics used, the respective strain, potency, dose, and duration data are shown only if available.

rious adverse events due to the administered probiotics organism and the absence of pathogenic growth in stool samples. Nineteen RCTs reported that no adverse events were judged to be associated with probiotics intake, the intervention was considered safe, or no adverse events were observed. Fifty-nine RCTs did not report on probiotics-specific adverse events.

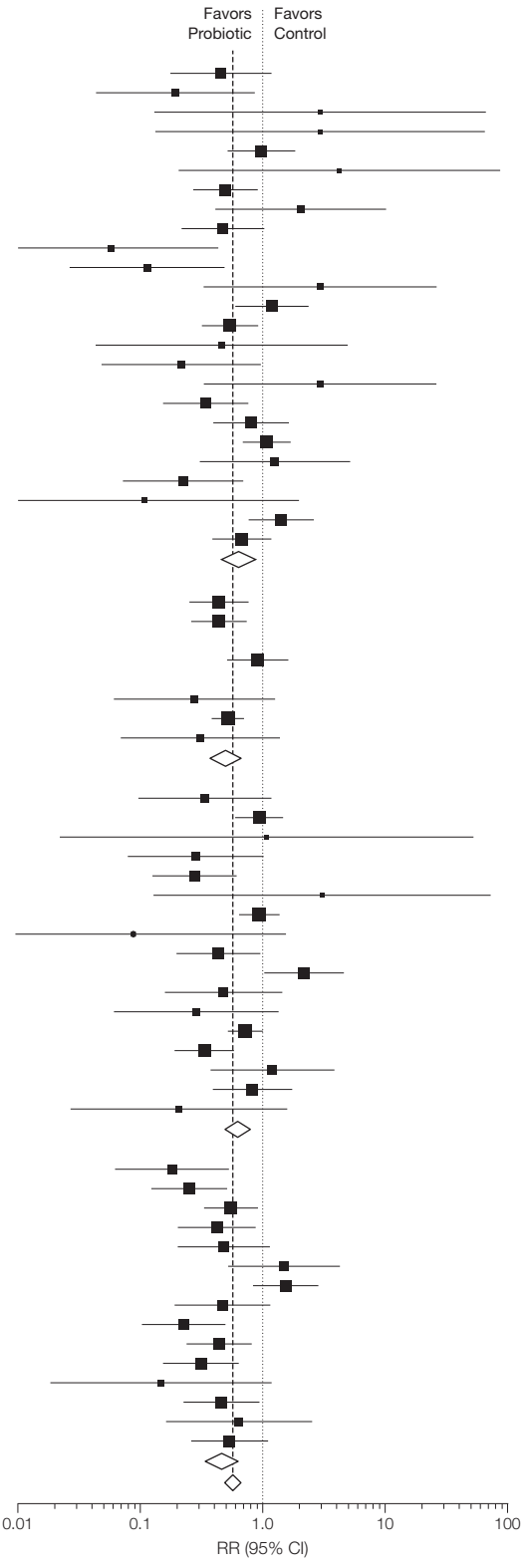
COMMENT

The principal finding of this review is that using probiotics as adjunct therapy reduces the risk of AAD, with an RR of 0.58. The result was consistent across a number of subgroup and sensitivity analyses. The treatment effect equates to an NNT of 13. The main limitations to this result are residual unexplained heterogeneity, poor documentation of the probiotic strains, and lack of assessment of probiotic-specific adverse events.

The existing evidence base for the prevention or treatment of AAD consists primarily of *Lactobacillus* interventions, either alone or in combination with other genera. Although RCTs of interventions of *Streptococcus, Enterococcus,* or *Bacillus* were eligible for inclusion in the review, few trials were identified. The included trials predominantly used lactic acid–producing bacteria such as *Lactobacillus rhamnosus,* or *L casei* with few exceptions, the *Saccharomyces* trials used the yeast *S boulardii [cerevisiae]*. The relative efficacy of probiotic interventions may be strain specific[81]; however, this analysis found no evidence that the effectiveness varies systematically even by probiotic genus. Most documented interventions used blends of genera, species, and strains, and interventions were poorly documented. Few trials described the strains used, and fewer indicated that the potency of the product was tested for the study.

In rare cases, probiotics have been linked to serious adverse effects such as fungemia[82-87] and bacterial sepsis[88]; hence, potential adverse effects of probiotics must be reviewed with the efficacy data, especially because little research attention has focused on adverse

Figure. Efficacy Results of Probiotic Use by Study



Study	No. With Antibiotic-Associated Diarrhea/No. in Group (%)		RR (95% CI)
	Intervention	Control	
Genus, Blend			
Jirapinyo,[20] 2002	3/8 (38)	8/10 (80)	0.47 (0.18-1.21)
Sheu,[57] 2002	2/80 (2)	10/80 (12)	0.20 (0.05-0.88)
Sullivan,[57] 2003	1/12 (8)	0/12 (0)	3.00 (0.13-66.80)
Lighthouse,[60] 2004	1/10 (10)	0/10 (0)	3.00 (0.14-65.55)
Plummer,[22] 2004	15/69 (22)	15/69 (22)	1.00 (0.53-1.88)
Schrezenmeir,[61] 2004	2/50 (4)	0/43 (0)	4.31 (0.21-87.30)
Corrêa,[18] 2005	13/87 (15)	24/82 (29)	0.51 (0.28-0.93)
Myllyluoma,[21] 2005	4/23 (17)	2/24 (8)	2.09 (0.42-10.32)
Conway,[64] 2007	9/149 (6)	17/137 (12)	0.49 (0.22-1.06)
de Bortoli,[65] 2007	1/105 (1)	16/101 (16)	0.06 (0.01-0.44)
Park,[66] 2007	2/176 (1)	17/176 (10)	0.12 (0.03-0.50)
Stein,[24] 2007	3/21 (14)	1/21 (5)	3.00 (0.34-26.56)
Kim,[67] 2008	16/168 (10)	14/179 (8)	1.22 (0.61-2.42)
Koning,[68] 2008	9/20 (45)	17/21 (81)	0.56 (0.33-0.94)
Szymański,[25] 2008	1/40 (2)	2/38 (5)	0.48 (0.04-5.03)
Wenus,[69] 2008	2/46 (4)	8/41 (20)	0.22 (0.05-0.99)
Engelbrektson,[70] 2009	3/20 (15)	1/20 (5)	3.00 (0.34-26.45)
Hickson,[19] 2007	7/69 (10)	19/66 (29)	0.35 (0.16-0.78)
Merenstein,[71] 2009	11/61 (18)	14/64 (22)	0.82 (0.41-1.67)
Koning,[72] 2010	13/17 (76)	9/13 (69)	1.10 (0.71-1.73)
de Vrese,[76] 2011	4/30 (13)	3/29 (10)	1.29 (0.32-5.26)
Saneeyan,[77] 2011	3/25 (12)	13/25 (52)	0.23 (0.07-0.71)
Selinger,[23] 2011	0/62 (0)	4/62 (6)	0.11 (0.01-2.02)
Yoon,[78] 2011	20/151 (13)	17/186 (9)	1.45 (0.79-2.67)
Bhalla,[38] 2011	19/176 (11)	26/167 (16)	0.69 (0.40-1.20)
Random effects model			**0.66 (0.49-0.88)**
Genus, *Bacillus*			
Li 2010,[73]	15/122 (12)	34/125 (27)	0.45 (0.26-0.79)
La Rosa,[43] 2003	14/60 (23)	31/60 (52)	0.45 (0.27-0.76)
Genus, *Bifidobacterium*			
Yasar,[75] 2010	14/38 (37)	15/38 (39)	0.93 (0.53-1.66)
Genus, *Enterococcus*			
Borgia,[5,3] 1982	2/40 (5)	7/40 (18)	0.29 (0.06-1.29)
Frigerio,[35] 1986	57/661 (9)	107/662 (16)	0.53 (0.39-0.72)
Wunderlich,[36] 1989	2/23 (9)	6/22 (27)	0.32 (0.07-1.41)
Random effects model			**0.51 (0.38-0.68)**
Genus, *Lactobacillus*			
Gotz,[33] 1979	3/48 (6)	9/50 (18)	0.35 (0.10-1.21)
Tankanow,[49] 1990	10/15 (67)	16/23 (70)	0.96 (0.61-1.50)
Reid,[54] 1992	0/19 (0)	0/21 (0)	1.10 (0.02-52.95)
Arvola,[37] 1999	3/89 (3)	9/78 (12)	0.29 (0.08-1.04)
Vanderhoof,[57] 1999	7/93 (8)	25/95 (26)	0.29 (0.13-0.63)
Felley,[56] 2001	1/26 (4)	0/27 (0)	3.11 (0.13-73.07)
Thomas,[50] 2001	39/152 (26)	40/150 (27)	0.96 (0.66-1.41)
Tursi,[62] 2004	0/35 (0)	5/35 (14)	0.09 (0.01-1.58)
Beausoleil,[17] 2007	7/44 (16)	16/45 (36)	0.45 (0.20-0.98)
Ruszczynski,[45] 2008	20/120 (17)	9/120 (8)	2.22 (1.06-4.68)
Safdar,[46] 2008	4/23 (17)	6/17 (35)	0.49 (0.16-1.48)
Szajewska,[48] 2009	2/44 (5)	6/39 (15)	0.30 (0.06-1.38)
Sampalis,[40] 2010	47/233 (20)	65/239 (27)	0.74 (0.53-1.03)
Gao,[41] 2010	13/86 (15)	37/84 (44)	0.34 (0.20-0.60)
Lönnermark,[44] 2010	6/118 (5)	5/121 (4)	1.23 (0.39-3.92)
Song,[47] 2010	11/103 (11)	14/111 (13)	0.85 (0.40-1.78)
Cimperman,[39] 2011	1/15 (7)	5/16 (3%)	0.21 (0.03-1.62)
Random effects model			**0.64 (0.47-0.86)**
Genus, *Saccharomyces*			
Ligny,[52] 1976	3/20 (15)	16/20 (80)	0.19 (0.06-0.54)
Adam,[26] 1977	9/199 (5)	33/189 (17)	0.26 (0.13-0.53)
Monteiro,[33] 1981	19/121 (16)	33/119 (28)	0.57 (0.34-0.94)
Surawicz,[34] 1989	11/116 (9)	14/64 (22)	0.43 (0.21-0.90)
McFarland,[32] 1995	7/97 (7)	14/96 (15)	0.49 (0.21-1.17)
Lewis,[31] 1998	7/33 (21)	5/36 (14)	1.53 (0.54-4.35)
Benhamou,[55] 1999	25/388 (6)	16/391 (4)	1.57 (0.85-2.90)
Erdeve,[59] 2004	7/127 (6)	12/105 (11)	0.48 (0.20-1.18)
Erdeve,[59] 2004	7/117 (6)	30/117 (26)	0.23 (0.11-0.51)
Duman,[63] 2005	14/204 (7)	28/185 (15)	0.45 (0.25-0.83)
Kotowska,[30] 2005	9/132 (7)	29/137 (21)	0.32 (0.16-0.65)
Can,[28] 2006	1/73 (1)	7/78 (9)	0.15 (0.02-1.21)
Cindoruk,[29] 2007	9/62 (15)	19/62 (31)	0.47 (0.23-0.96)
Bravo,[27] 2008	3/41 (7)	5/45 (11)	0.66 (0.17-2.58)
Song,[74] 2010	11/330 (3)	20/331 (6)	0.55 (0.27-1.13)
Random effects model			**0.48 (0.35-0.65)**
Overall random effects model			**0.58 (0.50-0.68)**

effects of probiotics used in clinical practice.[6] Although none of the included trials reported such adverse events, it is noteworthy that few trials addressed these outcomes, especially because cases of such infections suspected to be associated with the administered organisms were reported decades ago.[6]

The objective of this study was to evaluate broadly the available evidence on probiotic interventions for the prevention and treatment of AAD, building on previous nonsystematic overviews and systematic reviews on selected applications.[1,2,8,11,89-91] A large number of subgroup and sensitivity analyses were carried out to identify sources of statistical heterogeneity among trials. No systematic differences in results were identified across trials using different age groups, clinical indications, duration of antibiotics, included probiotics, and other study characteristics.

A substantial number of RCTs have addressed the prevention of AAD with probiotics; however, few trials were adequately powered. Trials aiming to demonstrate a reduction of a relatively rare event (probability 0.3) with an RR of 0.58 need sample sizes of 178 per group to achieve a power of 0.80. Only 10% of included trials fall into this category, suggesting the need for larger samples, eg, multisite trials.[92] Associations were shown through systematically identifying pertinent trials and pooling results across inadequately powered trials.

Determining which populations would benefit most from adjunct probiotics therapy[8] is an ongoing challenge; it must be considered that AAD does not occur in the majority of patients and when it occurs, it is usually self-limiting.[93] We identified only a small number of RCTs that targeted elderly participants, and more research is needed in particular for this participant group. Some antibiotics are more likely to cause diarrhea as an adverse effect,[94,95] but included studies rarely specified the antibiotics used or included patients taking a variety of different antibiotics, hindering an analysis of differential effectiveness by antibiotic taken.

A further limitation to this review is that we did not specifically solicit experts for published or unpublished research. Additional questions for future research include the optimal dose of the probiotic preparation and the comparative effectiveness of different probiotic interventions for the prevention or treatment of AAD. These questions should be explored in direct, head-to-head comparisons.

In summary, our review found sufficient evidence to conclude that adjunct probiotic administration is associated with a reduced risk of AAD. This generalized conclusion likely obscures heterogeneity in effectiveness among the patients, the antibiotics, and the probiotic strains or blends. Future studies should assess these factors and explicitly assess the possibility of adverse events to better refine our understanding of the use of probiotics to prevent AAD.

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Acquisition of data: Hempel, Newberry, Maher, Wang, Shanman, Johnsen.
Analysis and interpretation of data: Hempel, Newberry, Maher, Wang, Miles, Johnsen, Shekelle.
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