Probiotics for the prevention of antibiotic-associated diarrhea and *Clostridium difficile* infection among hospitalized patients: systematic review and meta-analysis

Reena Pattani, Valerie A Palda, Stephen W Hwang, Prakeshkumar S Shah

ABSTRACT

Background: Antibiotic-associated diarrhea (AAD) and *Clostridium difficile* infection (CDI) are associated with high morbidity, mortality, and health care costs. Probiotics may mitigate the existing disease burden. We performed a systematic review and meta-analysis to evaluate the efficacy of co-administration of probiotics with antibiotics in preventing these adverse outcomes in adult inpatients.

Methods: Systematic searches of MEDLINE (1946 to May 2012), Embase (1980 to May 2012), and the Cochrane Central Register of Controlled Trials were undertaken on May 31, 2012, to identify relevant publications. We searched for randomized controlled trials, published in English, of adult inpatients who were receiving antibiotics and who were randomly assigned to co-administration of probiotics or usual care, with or without the use of placebo. Studies were included if they reported on AAD or CDI (or both) as outcomes. Data for predetermined criteria evaluating study characteristics, methods, and risk of bias were extracted. Trials were given a global rating of good, fair, or poor by at least 2 reviewers. Meta-analyses were performed using a random-effects model, and pooled relative risks (RRs) and 95% confidence intervals (CIs) were calculated.

Results: Sixteen trials met the criteria for inclusion in this review. Four studies were of good quality, 5 were of fair quality, and 7 were of poor quality. Pooled analyses revealed significant reductions in the risks of AAD (RR 0.61, 95% CI 0.47 to 0.79) and CDI (RR 0.37, 95% CI 0.22 to 0.61) among patients randomly assigned to co-administration of probiotics. The number needed to treat for benefit was 11 (95% CI 8 to 20) for AAD and 14 (95% CI 9 to 50) for CDI. With subgroup analysis, significant reductions in rates of both AAD and CDI were retained in the subgroups of good-quality trials, the trials assessing a primarily *Lactobacillus*-based probiotic formulation, and the trials for which the follow-up period was less than 4 weeks.

Interpretation: Probiotics used concurrently with antibiotics reduce the risk of AAD and CDI.

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Competing interests: None declared.

Funding: No external funding was received for this review.

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➢ A rise in the use of antibiotics has resulted in a marked increase in antibiotic-associated diarrhea (AAD) and *Clostridium difficile* infection (CDI).[1] A spectrum of adverse sequelae is associated with CDI, including diarrhea, electrolyte abnormalities, sepsis and septic shock, toxic megacolon requiring colectomy, admission to the intensive care unit, and death.[2] In response to this devastating infection, a variety of non-

antibiotic strategies, such as toxin-binding agents, active immunization, intravenous administration of immune globulin, and fecal transplantation, have been attempted, with variable success.[3] Many hospitals are emphasizing infection control measures and antimicrobial stewardship to mitigate disease burden.[4] The concurrent administration of probiotics with antibiotics has also been studied as a potential preventive intervention against AAD and CDI.

Randomized controlled trials (RCTs) assessing probiotics for the prevention of AAD and CDI have been limited by low case volumes. Existing systematic reviews and meta-analyses[5–9] have grouped disparate populations, such as inpatients with outpatients or adults with children, and have considered clinically distinct entities, such as prevention and treatment of AAD and CDI, as combined outcomes.

Given the high morbidity among inpatients with these adverse outcomes, we conducted a systematic review and meta-analysis to evaluate the efficacy of probiotics administered with antibiotics in reducing these outcomes. We examined AAD and CDI as separate outcomes and limited our review to adult inpatients, because admission to hospital is a potent risk factor for colonization with *C. difficile*.[10]

Methods

Data sources and searches. This review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[11] We undertook systematic searches of MEDLINE (1946 to May 2012), Embase (1980 to May 2012), and the Cochrane Central Register of Controlled Trials on May 31, 2012, to identify relevant publications. We employed a sensitive search strategy (online Appendix A) using broad keywords to identify both the conditions of interest ("Clostridium difficile," "antibiotic-associated diarrhea," and phrase variants) and the intervention of interest ("probiotics" and the names of specific probiotic genera). We also performed a manual search of the reference lists of identified articles to identify and retrieve relevant research studies.

Study selection. One reviewer screened all abstracts for relevance to the topic. Two independent reviewers then screened the abstracts of relevant articles for possible inclusion. We included English-language RCTs of adult inpatients (i.e., patients who had been admitted to medical or surgical wards or to wards devoted to acute care of elderly patients) receiving antibiotics who were randomly assigned to co-administration of probiotics or to usual care, with or without the use of placebo. To be included in the review, a study must have reported the prevention of AAD or CDI (or both) as an outcome. The rate of AAD or CDI was defined as the number of patients who experienced diarrhea or diarrhea with *C. difficile* positivity by toxin assay or stool culture, respectively, while receiving antibiotics, divided by the number of patients with available end points. If an included publication did not report the necessary data, we contacted the primary authors to obtain original data for our quantitative analysis. If the authors of a study could not provide the necessary data, the study was included in the systematic review but was excluded from the meta-analysis. We excluded studies of probiotics used to prevent CDI recurrence in patients with a previous diagnosis of CDI. We also excluded trials in which antibiotics were used for eradication of *Helicobacter pylori*, as this represents a distinct clinical end point of treatment augmentation, and *H. pylori* infection is a condition for which management occurs almost exclusively in the outpatient setting. We excluded studies that were pilot trials of feasibility or tolerability because they did not define AAD or CDI incidence as outcomes of interest. We also excluded studies presented only at conferences, studies of before-and-after comparisons, and non-randomized comparison and cohort studies. Letters, commentaries, reviews, and editorials were excluded if they did not contain original data.

Data extraction and assessment of risk of bias. Two reviewers independently performed a full-text review of each included manuscript. Risk of bias in the included studies was assessed by the same 2 reviewers on the basis of the US Preventive Services Task Force recommendations, which include domains of randomization, blinding, comparability of groups, adequacy of follow-up (> 80%), clarity of interventions and outcomes, use of intention-to-treat analysis, and adequacy of study power.[12] A data extraction form was used to record the findings for each trial. The reviewers rated the studies as good, fair, or poor on the basis of a predetermined global quality rating scale combining the aforementioned criteria (see online Appendix B). Disagreement on quality rating was resolved by a third reviewer.

Data synthesis. Meta-analytic software (RevMan 5.0 from the Cochrane Collaboration) was used to synthesize the results. Relative risk (RR), risk difference (RD), and number needed to treat (NNT) to benefit or to harm,

with their respective 95% confidence intervals (CIs), were calculated using the DerSimonian Laird method. The Mantel–Haenszel method was used to weight the studies in the meta-analyses because the events being assessed were rare. We expected clinical and statistical heterogeneity among the studies. Therefore, we used the random-effects model for meta-analyses because it accounts for random variability both within and among studies. Subgroup analyses were planned *a priori* to assess the effect on results of study quality (good v. fair v. poor), type of probiotic (*Lactobacillus*-based v. *Saccharomyces boulardii*–based), and duration of follow-up (< 4 weeks or ≥ 4 weeks). No adjustments were made for multiple analyses. Post hoc meta-regression was performed to identify the independent effects of type of probiotics.

Heterogeneity and assessment of publication bias. Clinical heterogeneity was assessed for population characteristics, type of probiotic supplementation, and quality of studies. Statistical heterogeneity was assessed using the Cochrane Q test and by calculating *I*-squared (I^2) values. A funnel plot was created to assess the possibility of publication bias.

Ethics approval. All of the data are available from completed trials, and thus no ethics approval was necessary.

Results

Sixteen studies[13–28] were included in our analyses. Details of the selection process are shown in Figure 1, and the baseline characteristics of the studies are reported in Table 1. Only 5 of the studies involved more than one centre,[14,16–18,27] and the majority of studies were conducted in the United States or the United Kingdom. Among all of the trials, the range of mean ages for patients randomly assigned to probiotic was 33–79.9 years and to placebo was 33–78.5 years. Men constituted 43%–89% of participants in the probiotic groups and 40%–94.9% in the placebo group. However, the upper limit for proportion of men enrolled was influenced by just one study,[25] with the majority of studies including fewer than 75% men.

All of the studies, with one exception,[19] examined AAD as a primary outcome. Only 1 trial[18] assessed 2 end points of AAD with different definitions, and in that case, the definition that most closely approximated the outcome definitions in other studies was used for meta-analysis. One study[13] examined a dose–response relationship using a *Lactobacillus acidophilus* and *Lactobacillus casei* co-formulation. In that study, patients were randomly assigned to a high-dose probiotic group, a low-dose probiotic group, or a placebo group. For the purpose of this meta-analysis, we used the data from the low-dose and placebo groups, since that comparison most closely approximated the dosing regimens of the other included RCTs. Ten studies[13–15,17–20,23,24,28] used a *Lactobacillus*-based probiotic, 5 studies[16,21,22,25,26] evaluated *Saccharomyces boulardii,* and 1 study[27] assessed *Enterococcus* species. Twelve studies[13–17,19–22,24–26] sought to evaluate CDI as an outcome, with one having CDI as the primary end point.[19] Of the 12 studies evaluating CDI, 4 were initially excluded. Two of these studies[21,24] did not report CDI event rates because there were insufficient data to detect a difference. An additional 2 studies[16,20] reported CDI cases in ways that deviated from the original study protocols, and the outcome definitions were inconsistent with those of the other included studies. We contacted the primary authors of these 4 studies but were able to obtain original data for only one publication[24] to generate comparable outcome information. Therefore, all 4 of these studies were included in the systematic review, but only the single study for which original data were acquired[24] was ultimately included in the meta-analysis.

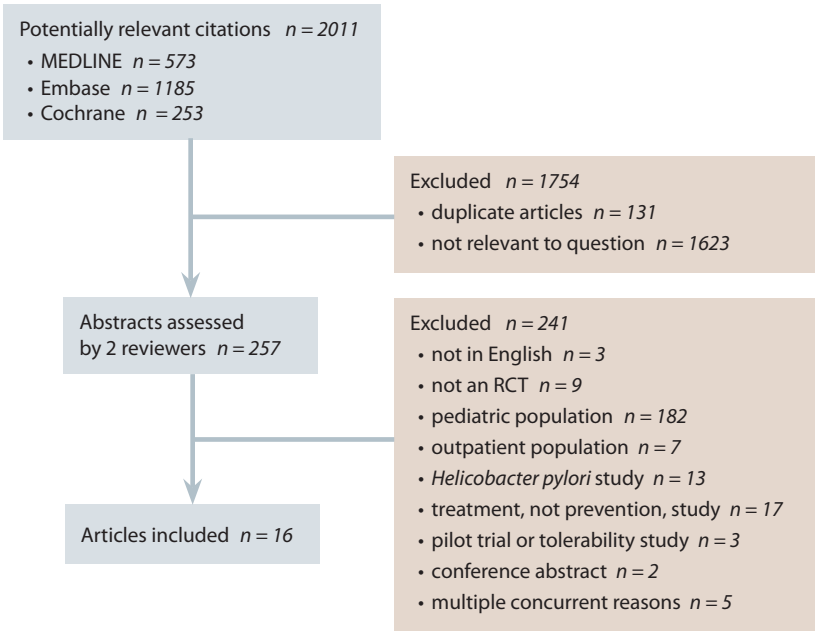


Figure 1
Flow diagram of study selection. Cochrane = Cochrane Central Register of Controlled Trials, RCT = randomized controlled trial.

Table 1

Characteristics of randomized controlled trials included in the meta-analysis

Source	Study population	Probiotic agent and duration	Additional follow-up	Primary and secondary outcomes	No. randomized total (probiotic, placebo)	No. analyzed, total (probiotic, placebo)	Attrition for primary outcome (%)
Good quality							
Gao et al.[13]	Adult inpatients Mean age 60 yr (both groups), 51% v. 50% men (probiotic v. placebo) Single centre, China	Lb-A, Lb-C within 36 h to 5 d after completion of antibiotics	21 d	AAD CDI	255 (high 86/ low 85, 84)*	AAD: 255 (high 86/low 85, 84) CDI: 255 (high 86/low 85, 84)	0
Hickson et al.[14]	Adult inpatients on orthopedic, medical, and care-of-the-elderly wards Mean age 73.7 v. 73.9 yr, 43% v. 48% men (probiotic v. placebo) 3 hospitals, United Kingdom	Lb-C, ST, Lb-B within 48 h to 7 d after completion of antibiotics	28 d	AAD CDI	135 (69, 66)	AAD: 113 (57, 56) CDI: 109 (56, 53)	16
Beausoleil et al.[15]	Adult inpatients Mean age 68.8 v. 72.9 yr, 45.5% v. 51.1% men (probiotic v. placebo) Single tertiary care centre, Canada	Lb-A, Lb-C within 48 h, for duration of antibiotics	21 d	AAD CDI	89 (44, 45)	AAD: 89 (44, 45) CDI: 89 (44, 45)	0
McFarland et al.[16]	Adult inpatients receiving at least one β-lactam antibiotic Mean age 40.7 v. 42.3 yr, 63.9% v. 65.6% men (probiotic v. placebo) 4 centres, United States	SB within 72 h to 3 d after completion of antibiotics	31–46 d	AAD CDI†	193 (97, 96)	AAD: 193 (97, 96) CDI: 24 (10, 14)	0
Fair quality							
Sampalis et al.[17]	Adult inpatients in emergency department or ward Mean age 59.5 v. 58.1 yr, 54.2% v. 48.4% men (probiotic v. placebo) 8 centres, Canada	Lb-A, Lb-C within 24 h to 5 d after completion of antibiotics	21 d	AAD CDI	472 (233, 239)	AAD: 437 (216, 221) CDI: 46 (16, 30)	8
Song et al.[18]	Adult inpatients Mean age 61 v. 60 yr, 61.2% v. 62.2% men (probiotic v. placebo) 10 tertiary care hospitals, Korea	Lb-A, Lb-R within 48 h for 14 d	14 d	AAD-1‡ AAD-2	214 (103, 111)	AAD-1: 214 (103, 111) AAD-2: 214 (103, 111)	0
Plummer et al.[19]	Adult inpatients on medical and care-of-the-elderly wards Baseline demographic characteristics not provided Single centre, United Kingdom	Lb-A, BB within 36 h for 20 d	0 d	CDI	138 (69, 69)	CDI: 138 (69, 69)	0
Thomas et al.[20]	Adult inpatients on medical ward Mean age 57.2 v. 54.4 yr, 51.1% v. 56.0% men (probiotic v. placebo) Single centre, United States	Lb-R within 24 h for 14 d	≥ 7 d	AAD CDI†	302 (152, 150)	AAD: 267 (133, 134) CDI: 267 (133, 134)	12
Lewis et al.[21]	Adult inpatients on medical ward Mean age 75 v. 77 yr (probiotic v. placebo), baseline sex ratio not provided Single centre, United Kingdom	SB within 24 h for duration of antibiotics	None	AAD CDI†	72 (not reported by group)	AAD: 69 (33, 36) CDI: 69 (33, 36)	4

Table 1 continued

Source	Study population	Probiotic agent and duration	Additional follow-up	Primary and secondary outcomes	No. randomized total (probiotic, placebo)	No. analyzed, total (probiotic, placebo)	Attrition for primary outcome (%)
Poor quality							
Pozzoni et al.[22]	Adult inpatients Mean age 79.9 v. 78.5 yr, 49.6% v. 50.0% men (probiotic v. placebo) Single centre, Italy	SB within 48 h for 7 d after completion of antibiotics	84 d	AAD CDI	275 (141, 134)	AAD: 204 (106, 98) CDI: 204 (106, 98)	26
Cimperman et al.[23]	Adult inpatients on medical wards Mean age 42.8 v. 63.6 yr, 54% v. 40% men (probiotic v. placebo) Single centre, United States	Lb-Reut within 96 h for 28 d	None	AAD	31 (15, 16)	23 (13, 10)	26
Wenus et al.[24]	Adult inpatients Mean age 58.8 v. 56.2 yr, 65.2% v. 51.2% men (probiotic v. placebo) Single centre, Norway	Lb-R, BB-12, Lb-A within 72 h for 14 d	None	AAD CDI	87 (46, 41)	AAD: 63 (34, 29) CDI: 55 (32, 23)	28
Can et al.[25]	Adult inpatients receiving chemo-therapy Mean age not provided, range 25–50 yr (both groups) 89.0% v. 94.9% men (probiotic v. placebo) Single centre, Turkey	SB within 48 h, duration not noted	28 d	AAD CDI	151 (73, 78)	AAD: 151 (73, 78) CDI: 151 (73, 78)	0
Surawicz et al.[26]	Adult inpatients Mean age 48.8 v. 45.4 yr, 66% v. 73% men (probiotic v. placebo) Single centre, United States	SB within 48 h to 14 d after completion of antibiotics	None	AAD CDI	318 (not reported by group)	AAD: 180 (116, 64) CDI: 138 (91, 47)	43
Wunderlich et al.[27]	Adult inpatients Mean age 33 yr overall, 48% men overall 5 centres, Switzerland	*Enterococcus* SF68 for 7 d	None	AAD	45 (23, 22)	45 (23, 22)	0
Gotz et al.[28]	Adult inpatients on medical wards receiving ampicillin Mean age 64 v. 65 yr, 36.1% v. 51.2% men (probiotic v. placebo) Single centre, United States	Lb-A, Lb-B within 24 h for 5 d	None	AAD	98 (48, 50)	AAD: 79 (36, 43)	19

AAD = antibiotic-associated diarrhea, BB = *Bifidobacterium bifidum*, BB-12 = *Bifidobacterium Bb-12*, CDI = *Clostridium difficile* infection, Lb-A = *Lactobacillus acidophilus*, Lb-B = *Lactobacillus bulgaricus*, Lb-C = *Lactobacillus casei*, Lb-R = *Lactobacillus rhamnosus*, Lb-Reut = *Lactobacillus reuteri*, SB = *Saccharomyces boulardii*, SF68 = *Enterococcus* SF68, ST = *Streptococcus thermophilus*.

* The study had 3 arms: high-dose probiotic, low-dose probiotic, and placebo; the low-dose arm was used for meta-analysis because it most closely approximated the intervention in other studies.

† Not included in the meta-analysis.

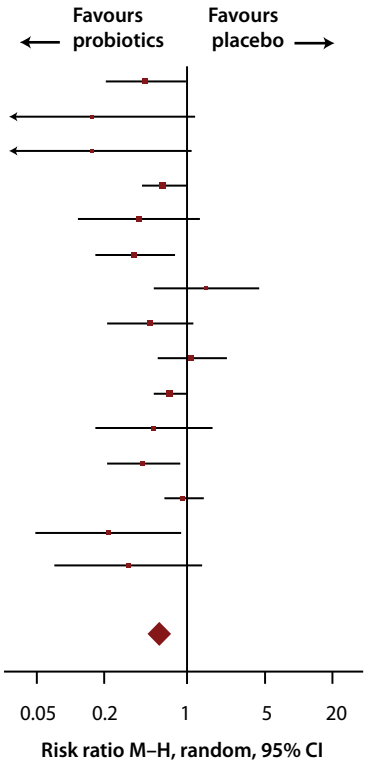
‡ Study had 2 end points of AAD with different definitions: AAD-1 = loose or watery stools more than 3 times per day for at least 2 days within 14 days of enrolment, AAD-2 = loose or watery stools more than 2 times per day for at least 2 days within 14 days of enrolment. The AAD-1 definition was used for meta-analysis because it most closely approximated the outcome definitions in other studies.

Meta-analysis of included studies demonstrated a statistically significant reduction in the risk of AAD (RR 0.61, 95% CI 0.47 to 0.79; I^2= 39%; RD −0.09, 95% CI −0.13 to −0.05; NNT to benefit 11, 95% CI 8 to 20). For CDI, there was a substantially lower number of patients with available end points. The event rates were 18 (3.1%) of 572 patients in the intervention arm and 55 (10.4%) of 527 patients in the placebo arm (RR 0.37, 95% CI 0.22 to 0.61; I^2= 0%; RD −0.07, 95% CI −0.11 to −0.02; NNT to benefit 14, 95% CI 9 to 50). The forest plots displaying the effect size by trial, as well as the aggregate effect size, are shown in Figure 2. Because of the small sample sizes and the rarity of outcomes, the CIs for several of the studies cross unity. Studies were heterogeneous in sample size, and the funnel plot (Figure 3) demonstrates a moderate degree of publication bias.

A

	Probiotics		Placebo			Risk ratio
Study or subgroup	Events	Total	Events	Total	Weight, %	M–H, random, 95% CI
Beausoleil et al.[15]	7	44	16	45	7.0	0.45 (0.20–0.98)
Can et al.[25]	1	73	7	78	1.4	0.15 (0.02–1.21)
Cimperman et al.[23]	1	13	5	10	1.5	0.15 (0.02–1.12)
Gao et al.[13]	24	85	37	84	13.5	0.64 (0.42–0.97)
Gotz et al.[28]	3	36	9	43	3.5	0.40 (0.12–1.36)
Hickson et al.[14]	7	57	19	56	7.0	0.36 (0.17–0.79)
Lewis et al.[21]	7	33	5	36	4.6	1.53 (0.54–4.35)
McFarland et al.[16]	7	97	14	96	6.1	0.49 (0.21–1.17)
Pozzoni et al.[22]	16	106	13	98	8.4	1.14 (0.58–2.24)
Sampalis et al.[17]	47	216	65	221	15.7	0.74 (0.53–1.02)
Song et al.[18]	4	103	8	111	3.8	0.54 (0.17–1.74)
Surawicz et al.[26]	11	116	14	64	7.7	0.43 (0.21–0.90)
Thomas et al.[20]	39	133	40	134	14.6	0.98 (0.68–1.42)
Wenus et al.[24]	2	34	8	29	2.6	0.21 (0.05–0.93)
Wunderlich et al.[27]	2	23	6	22	2.5	0.32 (0.07–1.41)
Overall	**178**	**1169**	**266**	**1127**	**100.0**	**0.61 (0.47–0.79)**

Heterogeneity: tau² = 0.08; chi² = 22.89, df = 14 (p = 0.06), I^2 = 39%
Test for overall effect: Z = 3.83 (p = 0.0001)



B

	Probiotics		Placebo			Risk ratio
Study or subgroup	Events	Total	Events	Total	Weight, %	M–H, random, 95% CI
Beausoleil et al.[15]	1	44	7	45	6.3	0.15 (0.02–1.14)
Can et al.[25]	0	73	2	78	2.9	0.21 (0.01–4.37)
Gao et al.[13]	8	85	20	84	45.9	0.40 (0.18–0.85)
Hickson et al.[14]	0	56	9	53	3.4	0.05 (0.00–0.84)
Plummer et al.[19]	2	69	5	69	10.4	0.40 (0.08–1.99)
Pozzoni et al.[22]	3	106	2	98	8.5	1.39 (0.24–8.13)
Sampalis et al.[17]	1	16	4	30	6.0	0.47 (0.06–3.85)
Surawicz et al.[26]	3	91	5	47	13.9	0.31 (0.08–1.24)
Wenus et al.[24]	0	32	1	23	2.7	0.24 (0.01–5.70)
Overall	**18**	**572**	**55**	**527**	**100.0**	**0.37 (0.22–0.61)**

Heterogeneity: tau² = 0.00; chi² = 5.42, df = 8 (p = 0.71), I^2 = 0%
Test for overall effect: Z = 3.82 (p = 0.0001)

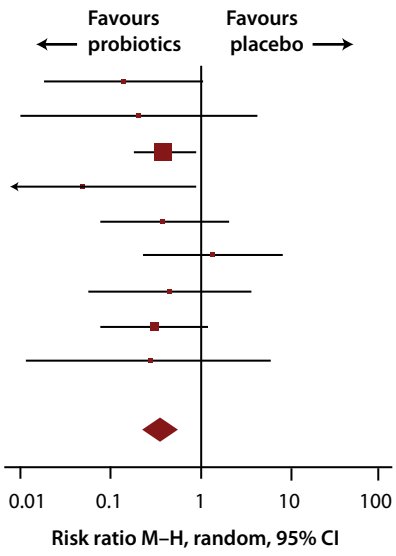


Figure 2
Meta-analysis of all randomized controlled trials demonstrating the effect of probiotics on (A) antibiotic-associated diarrhea and (B) *Clostridium difficile* infection. M–H = Mantel–Haenszel weighting.

Four of the studies[13–16] were rated as having good quality, whereas 5 studies were of fair quality[17–21] and 7 were of poor quality[22–28] (Table 2).

When the results were stratified by study quality (Table 3), the 4 good-quality studies[13–16] demonstrated reduction in AAD and CDI with the use of probiotics. These studies shared features that led to their high rating, specifically clear inclusion criteria, interventions, and outcomes. They used validated scales or precise qualitative explanations to define the outcome measures and had reasonably long-term follow-up (between 3 and 7 weeks). The fair-quality studies,[17–21] when pooled, demonstrated reduction in AAD and CDI that was not statistically significant. These studies received lower quality ratings because of a lack of clarity or validity in their outcome measures, with the use of liberal, subjective criteria for AAD and CDI that may have resulted in overreporting. Specifically for CDI, 2 of the studies[19,21] involved testing for *C. difficile* toxin on formed stool, which may have led to the inclusion of cases of *C. difficile* colonization as opposed to the clinically relevant outcome of CDI. All but one[22] of the 7 poor-quality studies[22–28] showed a significantly lower RR for AAD with the use of probiotics. Four of the poor-quality trials[22,24–26] assessed CDI as a secondary outcome, but none of them demonstrated a significant risk reduction. In general, the poor-quality studies were limited by unclear interventions and outcomes (see Table 2). They lacked formal reporting of key study methods, such as the randomization process, blinding methods, and the duration of the intervention or follow-up.

When studies were pooled by type of probiotic, reductions in AAD and CDI were observed regardless of whether a primarily *Lactobacillus*-based probiotic or an *S. boulardii*–based formulation was used. However, only the combined analyses of *Lactobacillus*-based formulations showed reductions that were statistically significant. The similarity in effect size between the 2 groups has some biologic plausibility, given that the benefit of probiotics is thought to derive, at least in part, from recolonization of the gastrointestinal tract with "normal," non-pathogenic flora, rather than from species-specific effects.[29]

For short follow-up periods (< 4 weeks), statistically significant reductions in both AAD and CDI were observed. With longer follow-up, only the reduction in AAD, and not that for CDI, remained significant. Statistical heterogeneity (I^2) was moderately greater for the subgroup of patients with follow-up of 4 weeks or longer (54% for AAD and 57% for CDI). The literature suggests that AAD and CDI can occur after just one dose of antibiotics and may appear up to several weeks after completion of antibiotic therapy.[30] As such, an adequate follow-up period is needed to ensure that most cases are appropriately identified. Our subgroup analysis by follow-up period was dichotomized as less than 4 weeks v. 4 weeks or more, because this time frame reflects a practical and clinically applicable cut-off for ongoing patient surveillance.

Post hoc meta-regression analysis by type of probiotic confirmed the findings of the subgroup analysis. Specifically, the primarily *Lactobacillus*-based formulation remained significantly effective in reducing AAD. Because of wide variability in the duration of follow-up, we were unable to perform meta-regression of duration of follow-up as a continuous measure.

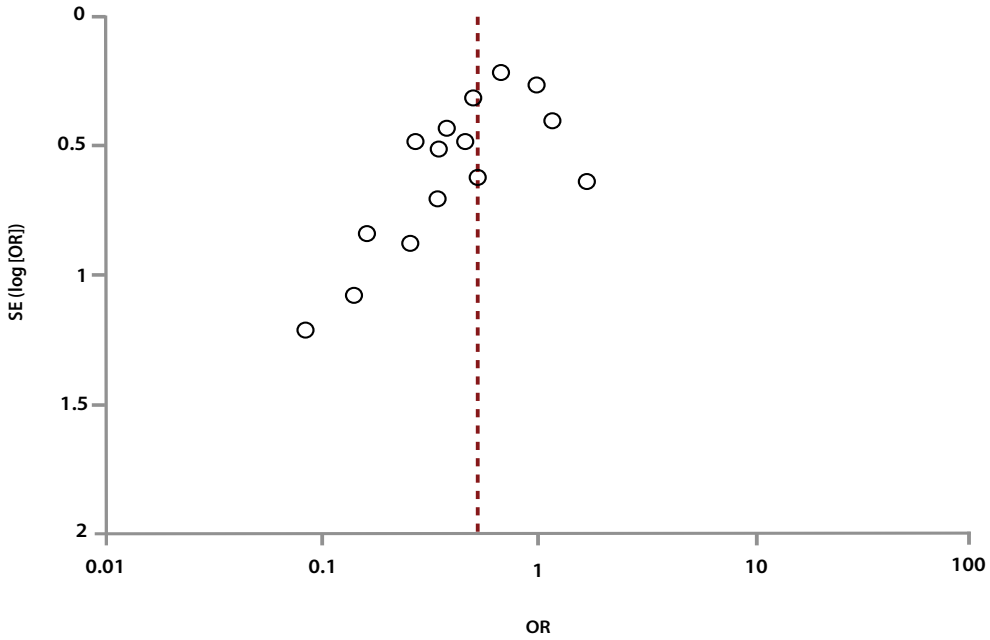


Figure 3
Funnel plot of 15 studies included in the meta-analysis for the outcome of antibiotic-associated diarrhea demonstrates moderate publication bias. OR = odds ratio, SE = standard error.

Table 2

Quality ratings for randomized controlled trials included in the systematic review, based on criteria of the US Preventive Services Task Force[12]

Trial	Randomized	Blinded	Comparable groups (start and end)	Follow-up > 80%	Clear interventions	Clear, relevant outcomes	Valid, reliable, equal measures	Intention-to-treat analysis	Confounders noted	Appropriate power calculation reported
Good quality										
Gao et al.[13]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hickson et al.[14]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Beausoleil et al.[15]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
McFarland et al.[16]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Fair quality										
Sampalis et al.[17]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No
Song et al.[18]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Plummer et al.[19]	Yes	Yes	Not reported	Yes	Yes	Yes	Yes	Yes	No	No
Thomas et al.[20]	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No
Lewis et al.[21]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No
Poor quality										
Pozzoni et al.[22]	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No
Cimperman et al.[23]	Yes	Yes	No	No	Yes	Yes	Yes	No	No	No
Wenus et al.[24]	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Can et al.[25]	Yes	Yes	Not reported	Yes	Yes	Yes	No	Yes	No	No
Surawicz et al.[26]	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes
Wunderlich et al.[27]	Yes*	Yes*	Yes*	Yes	Yes	Yes	Yes	Yes	No	No
Gotz et al.[28]	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No

* Details not provided.

Table 3
Subgroup analyses

Subgroup	No. of studies	No. of events/no. of patients analyzed		RR (95% CI)	RD (95% CI)	I^2 (%)
		Probiotic group	Placebo group			
AAD						
All studies	15	178/1169	266/1127	0.61 (0.47 to 0.79)	–0.09 (–0.13 to –0.05)	39
Study quality						
Good	4	45/283	86/281	0.54 (0.39 to 0.73)	–0.14 (–0.21 to –0.06)	0
Fair	4	97/485	118/502	0.85 (0.67 to 1.08)	–0.03 (–0.08 to 0.01)	3
Poor	7	36/401	62/344	0.42 (0.23 to 0.76)	–0.11 (–0.18 to –0.04)	42
Probiotic type*						
Lactobacillus	9	134/721	207/733	0.64 (0.48 to 0.84)	–0.11 (–0.17 to –0.04)	35
Saccharomyces boulardii	5	42/425	53/372	0.68 (0.37 to 1.24)	–0.05 (–0.11 to 0.00)	53
Follow-up						
< 4 wk	10	146/823	208/789	0.57 (0.41 to 0.79)	–0.09 (–0.14 to –0.04)	29
≥ 4 wk	5	32/346	58/338	0.47 (0.23 to 0.94)	–0.09 (–0.18 to –0.01)	54
CDI						
All studies	9	18/574	55/533	0.37 (0.22 to 0.62)	–0.07 (–0.12 to –0.02)	0
Study quality						
Good	3	9/185	36/182	0.24 (0.08 to 0.73)	–0.15 (–0.21 to –0.09)	29
Fair	2	3/85	9/99	0.42 (0.12 to 1.52)	–0.05 (–0.11 to 0.02)	0
Poor	4	6/302	10/246	0.46 (0.17 to 1.22)	–0.02 (–0.05 to 0.01)	0
Probiotic type						
Lactobacillus	6	12/302	46/304	0.33 (0.18 to 0.60)	–0.10 (–0.15 to –0.05)	0
Saccharomyces boulardii	3	6/270	9/223	0.49 (0.17 to 1.40)	–0.02 (–0.06 to 0.02)	2
Follow-up						
< 4 wk	6	15/337	42/298	0.35 (0.20 to 0.62)	–0.08 (–0.12 to –0.04)	0
≥ 4 wk	3	3/235	13/229	0.31 (0.03 to 2.77)	–0.05 (–0.13 to 0.03)	57

AAD = antibiotic-associated diarrhea, CDI = *Clostridium difficile* infection, CI = confidence interval, RD = risk difference, RR = relative risk.
*One study (Wunderlich et al.[27]) was not included in the subgroup analysis by probiotic type because it was the only study to use a single *Enterococcus* species formulation.

No life-threatening adverse effects of probiotics were reported in these RCTs. Despite case reports of toxic effects among patients with extenuating circumstances,[31–33] probiotics had an excellent safety profile, the most common adverse effect being gastrointestinal upset.

Interpretation

Probiotics can confer health benefits in several ways: by creating nutrient competition, by favourably altering the gut flora, by serving as a barrier against pathogen-receptor binding, by elaborating immunomodulators (such as immunoglobulin A) or trophic factors, and by reducing osmotic diarrhea.[34] With recent epidemiologic patterns showing a rise in the occurrence of AAD and CDI among healthier, previously spared populations, as well as among those patients most vulnerable to its complications,[35–37] there is an urgent need to find innovative methods for prevention.

Our findings indicate that probiotics given concurrently with antibiotics reduce the risk of AAD and CDI. The results of our meta-analysis are concordant with several prior systematic reviews and meta-analyses,[5–9] which varied in terms of the patients assessed and the outcomes defined. In a recent meta-analysis, Hempel et al.[8] assessed probiotics for both the prevention and the treatment of AAD and reported benefit. Those authors included 82 trials of significant heterogeneity: in addition to examining both prevention and treatment trials, they assessed trials involving both inpatients and outpatients, they evaluated all age groups, and they included 24 trials in which patients were receiving antibiotics for *H. pylori* eradication.

One of the strengths of our review was our emphasis on ensuring that comparable outcome definitions were used in the meta-analysis. We achieved this comparability by carefully selecting the study arms to include

for trials with more than 2 intervention groups and by contacting primary authors for original data when needed. These actions mitigated some of the impact of the clinical heterogeneity among the trials. Another major strength was our focus on a specific patient population: inpatients. Reducing the incidence of CDI will improve individual patient outcomes while curtailing spread in the high-risk setting of hospitals. Thus, these results have implications for the health of other, non-infected inpatients. Finally, our meta-analysis showed that benefit was retained regardless of study quality, type of probiotic used, and duration of follow-up. However, the results were only significant for both AAD and CDI concurrently for the subgroups of good-quality studies, studies assessing *Lactobacillus*-based formulations, and studies in which the follow-up was less than 4 weeks.

Several limitations in the individual studies and in our meta-analysis merit discussion. A notable limitation among some of the more recent studies was the high baseline rates of AAD and CDI in the placebo arms. Three of the recent RCTs, all of which were assessed as being of good quality,[13–15] reported AAD rates of 34%–44% and CDI rates of 16%–24% in the control groups. These high baseline event rates may have facilitated the detection of a significant effect size despite small sample sizes. The extent to which this result may have been influenced by different local practices in antimicrobial stewardship and environmental infection control is unknown, and thus their effect sizes may not be replicated in other settings where baseline rates of AAD and CDI are lower.

The included trials shared certain methodological issues that also limited broad interpretation of the results. Some of the studies had lower enrolment than planned for detecting the expected differences, a factor of particular importance for the negative trials.[20,21] Almost all of the studies that we assessed excluded patients who might otherwise be considered candidates for a hospital-wide intervention like probiotics. For example, patients who had received a course of antibiotics on an outpatient basis in the weeks preceding trial enrolment were excluded to avoid inclusion of cases of community-associated CDI. Furthermore, patients with pre-existing gastrointestinal pathology were excluded to avoid inclusion of patients suffering from diarrhea not related to antibiotics. These steps may limit the interpretation of how probiotics will affect a more inclusive inpatient population. Two of the fair-quality studies[18,21] reported possible probiotic under-dosing. A high rate of attrition (> 20%) was observed in 4 studies,[22–24,26] which necessitated a poor quality rating.

Our meta-analysis also suffered from some important limitations. There was evidence of moderate publication bias (see Figure 3). Three trials were excluded because they were not in English.[38–40] Furthermore, among all of the patients assessed for AAD, 1200 patients did not have end points for CDI.

We chose to convey outcome information using RDs and NNTs. We acknowledge the limitation of using NNTs to convey outcome information, given the clinical and statistical heterogeneity among the studies included in this review. Admittedly, NNT is difficult to interpret when such heterogeneity exists, and we therefore caution readers and decision-makers against using this information without putting it in the context of the study variability and considering the local prevalence of CDI in their respective populations of interest.

Conclusions. Our findings illuminate the benefits of probiotics in preventing both AAD and CDI in the specific patient population of adult inpatients requiring antibiotics. On the basis of the current review, probiotics can be recommended for such patients in the absence of contraindications; however, the prevalence of AAD and CDI should be taken into consideration before guidelines are developed. The literature does not clearly indicate a favoured choice of probiotic, although there is stronger evidence for *Lactobacillus*-based formulations.

Many health care providers have been hesitant to adopt probiotics in routine practice, despite impressive effect sizes. This may be because of the small sample sizes in the individual trials, the high baseline rates of AAD and CDI in the larger, more recent trials, the clinical and statistical heterogeneity between trials, and the publication bias seen in this and other meta-analyses. While there may be a signal toward clinical improvement with this intervention, future RCTs should strive to recruit more patients and to strengthen their power to help bring probiotics to the bedside. Other research that will add to our current knowledge in this area might address whether there is greater benefit with the use of combination therapy over single-species probiotic formulations. The hypothesis of a dose–response effect requires further validation.

Contributors: Reena Pattani participated in designing the study methodology, contributed to data extraction and analysis, and was the principal writer of the manuscript. Valerie A. Palda conceived the project, out-

lined the qualitative study methods, and contributed to data extraction and analysis. Stephen W. Hwang assisted in designing the study methods and in extracting and analyzing the data. Prakeshkumar S. Shah outlined quantitative methods, conducted the quantitative analysis, and participated in writing the manuscript. All of the authors reviewed and edited drafts of the manuscript for important intellectual content, and each author approved the final version of the manuscript.

Acknowledgments: We thank Elizabeth Uleryk, MLS, Director of Hospital Library and Archives, The Hospital for Sick Children, for her help in developing the search strategy, undertaking the search, and writing the section on literature search methods in online Appendix A.

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Published: 4 June 2013

Citation: Pattani R, Palda VA, Hwang SW, Shah PS. Probiotics for the prevention of antibiotic-associated diarrhea and *Clostridium difficile* infection among hospitalized patients: systematic review and meta-analysis. *Open Med* 2013;7(2):e56–e67.