PROBIOTICS IN THE PREVENTION OF ANTIBIOTIC-ASSOCIATED DIARRHEA IN CHILDREN: A META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

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Objective To systematically evaluate the effectiveness of probiotics in preventing antibiotic-associated diarrhea (AAD) in children.

Study design The following electronic databases up to December 2005, in any language, were searched for studies relevant to AAD and probiotics: MEDLINE, EMBASE, and The Cochrane Library. Only randomized controlled trials (RCT) were considered for study inclusion.

Results Six placebo-controlled, RCTs (766 children) were included. Treatment with probiotics compared with placebo reduced the risk of AAD from 28.5% to 11.9% (relative risk, RR, 0.44, 95% CI 0.25 to 0.77, random effect model). Preplanned subgroup analysis showed that reduction of the risk of AAD was associated with the use of *Lactobacillus* GG (2 RCTs, 307 participants, RR 0.3, 95% CI 0.15 to 0.6), *S. boulardii* (1 RCT, 246 participants, RR 0.2, 95% CI 0.07-0.6), or *B. lactis* & *Str. thermophilus* (1 RCT, 157 participants, RR 0.5, 95% CI 0.3 to 0.95).

Conclusions Probiotics reduce the risk of AAD in children. For every 7 patients that would develop diarrhea while being treated with antibiotics, one fewer will develop AAD if also receiving probiotics. *(J Pediatr 2006;149:367-72)*

Although the use of antibiotics in primary care in Europe varied greatly, antibiotics are prescribed commonly in many countries. The highest rate of use was in France (32.2 defined daily doses [DDD] per 1000 inhabitants per day), and the lowest rate of use was in the Netherlands (10.0 DDD per 1000 inhabitants daily).[1] In Poland, outpatient antibiotic use is at the level of approximately 22.0 DDD per 1000 inhabitants. Children are the main antibiotic consumers, with usage rates 3 times higher than that of older patients.[2] In most countries, an increasing use of newer broad-spectrum antibiotics has been observed, such as the combination of amoxicillin and clavulanic acid, the new macrolides, and quinolones, with decrease in use of older narrow-spectrum penicillins and cephalosporins.[1]

A common side effect is antibiotic-associated diarrhea (AAD) defined as otherwise unexplained diarrhea that occurs in association with the administration of antibiotics.[3] In the pediatric population, AAD occurs in 11-40% of children between the initiation of therapy and up to 2 months after cessation of treatment.[4,5] Although no infectious agent is found in most cases, the bacterial agent commonly associated with AAD, particularly in the most severe episodes (pseudomembranous colitis), is *Clostridium difficile*.[6] Almost all antibiotics, particularly those active against anaerobes, can cause diarrhea, but the risk seems to be higher with aminopenicillins, the combination of aminopenicillins and clavulanate, cephalosporins, and clindamycin.[7,8]

Preventive measures include the use of probiotics, which are live microbial food ingredients that are beneficial to health.[9] The rationale for the use of probiotics in AAD is based on the assumption that in some instances diarrhea is associated with disturbance in the normal intestinal microflora.[10] At least four systematic reviews (with or without meta-analysis) have shown that some probiotic strains are associated with a decrease of AAD.[11-14] It is unclear whether similar benefits occur in children, as most of the studies included in the meta-analyses were conducted in adults. With conflicting data about the effects of *Lactobacillus rhamnosus* GG suggesting a different response in adult[15] and pediatric populations,[16,17] extrapolation of data to children remains speculative. Our aim was to identify and review evidence on the effectiveness and safety of using probiotics in children to prevent AAD. If probiotics are effective in children, another aim was to determine which probiotic strain is most effective.

AAD	Antibiotic-associated diarrhea	NNT	Number needed to treat
CI	Confidence interval	RCT	Randomized controlled trial
DDD	Defined daily dose	RR	Relative risk

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METHODS

Search strategy

We searched: MEDLINE (1966 – December 2005), EMBASE (1980 – December 2005), Cumulative Index to Nursing and Allied Health (CINAHL, 1982 – December 2005), The Cochrane Database of Systematic Reviews (Issue 2, 2005), and The Cochrane Controlled Trials Register (CENTRAL) (Issue 4, 2005). The search strategy included use of a validated filter for identifying controlled trials,[18] which was combined with a topic-specific strategy.

In brief, the search combined terms related to diarrhea (diarrhea/diarrhoea, antibiotic-associated/antibiotic associated, *Clostridium difficile*) with terms related to probiotics (probiotic*, lactobacill*, lactococc*, bifidobacter*, enterococc*, streptococc*, *Saccharomyces*) using Boolean operators and database specific syntax. Furthermore, reference lists from the original studies and review articles identified were screened. No limit was imposed regarding the language of publication, but certain publication types (i.e., letters to the editor, abstracts, proceedings from scientific meetings) were excluded. We considered randomized controlled trials (RCTs) in children who had received antibiotics for any reason in any setting (out- or inpatient) in which the use of probiotics at any dose or time schedule was assessed and compared with placebo or with no additional intervention. We excluded studies of adults.

Procedures

Two reviewers independently applied inclusion criteria to all identified and retrieved articles. The same reviewers extracted data from included studies on standard data extraction forms. Discrepancies between reviewers were resolved by discussion. For dichotomous outcomes, we extracted the total number of participants and the number of participants who experienced the event. For continuous outcomes, we extracted the total number of participants, means, and standard deviations. We compared the extracted data to identify errors. One reviewer (HS) entered the data into The Cochrane Review Manager (RevMan [Computer program]. Version 4.2 for Windows. Oxford, England: The Cochrane Collaboration, 2003) for analysis.

We used standard criteria (allocation concealment, blinding, intention-to-treat analysis, loss to follow-up) to appraise the methodologic quality of the studies. Trial quality was classified subjectively as low, medium, or high risk of bias. We assigned risk of bias categories on the basis of the number of items judged inadequate in each study: low risk of bias (up to one inadequate item); medium risk of bias (up to 3 inadequate items); high risk of bias (more than 3 inadequate items); very high risk of bias (no description of methods).

The *primary* outcomes were the incidence of diarrhea or AAD (as defined by the investigators) and the incidence of *C. difficile* diarrhea. We also assessed the following *secondary* outcomes: mean duration of diarrhea, the need for discontinuation of the antibiotic treatment, hospitalization to manage the diarrhea (in outpatients) or intravenous rehydration in any of the study groups, and adverse events.

Table II. Characteristics of the excluded studies

Study	Reason(s) for exclusion
Seki et al[25]	Nonrandomized, clinical trial
La Rosa et al[26]	RCT; explored the effect of *Lactobacillus sporogens* but given with fructo-oligosaccharides compared with placebo in the prevention of AAD
Erdeve et al[24]	Nonrandomized, clinical trial

RCT, randomized controlled trial.

Statistical analysis

For dichotomous outcomes, relative risks with 95% confidence interval (CI) were calculated in RevMan for individual studies. Number needed to treat (NNT) with 95% CI was calculated using the computer software StatsDirect (1,9,12 (2002-05011); Iain E. Buchan). Summary statistics were calculated with either a fixed-effects or random-effects model approach according to the heterogeneity in outcomes across studies. Weights given to each study are based on the inverse of the variance. Heterogeneity was analyzed by Cochran Q statistic with $\alpha=0.05$ for statistical significance and by the statistic I^2, which is derived from Q and describes the proportion of total variation that is due to heterogeneity beyond chance.[19] A value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity. To explore clinical differences between trials that might be expected to influence the size of the treatment effect for the primary outcomes, a priori defined subgroup analyses were performed based on factors that potentially could influence the magnitude of the treatment effect: (1) probiotic strain; (2) definition of diarrhea; (3) type of antibiotic used. We also conducted sensitivity analyses according to each of the parameters of trial methodological quality. We took no formal steps to look for publication bias, such as plotting effect sizes or calculating test statistics; there were few studies on any given effect, and any formal method would have had little power.

RESULTS

Description of studies

We initially identified 9 articles. Table I (available at www.jpeds.com) summarizes the characteristics of the 6 included trials.[16,17,20-23] The remaining 3 studies were excluded. Table II summarizes characteristics of the excluded trials,[24-26] including the reasons for exclusion.

The 6 selected studies recruited a total of 766 participants (376 in the experimental group and 390 in the control group) who completed the follow-up interval. All studies were placebo controlled. There was considerable clinical heterogeneity among the trials in sample size (from 18 to 269 participants), settings (inpatients or outpatients), age of children,

Table III. Methodological quality of included trials

Trial	Generation of randomization	Allocation concealment*	Blinding	Intention-to-treat analysis†	Completeness of follow-up‡	Risk of bias
Tankanov et al[21]	Not described	Unclear	Yes	No	63% (38/60)	High
Jirapinyo et al[22]	Randomization list (but no details are reported)	Unclear	Yes	Yes	100% (18/18)	Medium
Correa et al[23]	Methods not reported	Unclear	Yes	No	93% (157/169)	Medium
Arvola et al[17]	Computer randomization	Adequate	Yes	No	71% (119/167)	Medium
Vanderhoof et al[16]	Computer-generated randomization list	Adequate	Yes	No	93% (188/202)	Low
Kotowska et al[20]	Block randomization due to computer-generated randomization list	Adequate	Yes	Yes	91% (246/269)	Low

*Allocation concealment: Adequate-Randomization method described that would not allow investigator/caregivers to identify or influence the intervention group before eligible participants entered the study; Unclear-Randomization stated, but no information about method used was provided.
†Intention-to-treat analysis: Yes: Specifically reported by authors that intention-to-treat analysis was undertaken and this was confirmed by our study assessment; Yes: Not stated, but confirmed by our study assessment; No: Not reported and lack of intention-to-treat analysis confirmed by our study assessment. No: Stated, but not confirmed by our study assessment.
‡Completeness of follow-up: Trials with >80% follow-up of participants.

probiotic strain(s) used and daily dose of the study product, and the type of antibiotics administered. All trials had a relatively short follow-up, and in one trial it was not specified. Furthermore, there was variability in definitions of outcome measures. The most commonly used definition of diarrhea was the presence of 3 or more loose (or watery) stools, but criteria for its duration varied from 24 hours to at least 48 hours. In one trial the definition of diarrhea was not stated.

Table III shows results of the methodologic quality assessment of included studies. Allocation concealment was adequate in only 3 trials. Although all were double-blind studies, it often was not stated who was blinded. Intention-to treat-analysis was performed in only 2 trials. Completeness of follow-up was inadequate in 2 trials. The probiotics studied were well tolerated, and no adverse events clearly associated with this therapy were reported.

Prevention of diarrhea

Treatment with probiotics compared with placebo reduced the risk of diarrhea in patients treated with antibiotics (as defined by the study investigators) from 28.5% to 11.97% (RR 0.43, 95% CI 0.31 to 0.58, fixed effect model; 0.44, 95% CI 0.25 to 0.77, random effect model) (Figure). For every 7 patients receiving daily probiotics with antibiotics, one fewer would develop diarrhea (NNT 7, 95% CI 5-10).

The statistical test of homogeneity yielded a significant result (chi-square = 16.47, $P = 0.006$, I^2=69.6%). Significant heterogeneity was attributable to the inclusion of the study[21] with a high risk of bias (no description of methods, incompleteness of follow-up). Exclusion of this trial (which in addition used a definition of diarrhea that differed considerably from those used by other investigators) resulted in a homogenous group of 5 studies involving 728 patients (chi-square = 3.62, $P = 0.46$, I^2=0%). The significance of the pooled effect of probiotics remained when calculations were made with 5 homogenous trials only (RR 0.35, 95% CI 0.24 to 0.51, fixed effect model).

The Figure shows results of the preplanned subgroup analysis based on the probiotic type. The reduction of the risk of AAD was associated with the use of *Lactobacillus* GG (2 RCT, 307 participants, RR 0.3, 95% CI 0.15 to 0.6, NNT 6, 95% CI: 4–13), *Saccharomyces boulardii* (1 RCT, 246 participants, RR 0.2, 95% CI 0.07-0.6, NNT 8, 95% CI 5-15), or *B. lactis & Streptococcus thermophilus* (1 RCT, 157 participants, RR 0.5, 95% CI 0.3 to 0.95, NNT 7, 95% CI 4-62). In contrast, the use of either *L. acidophilus/Bifidobacterium infantis* (1 RCT, 18 participants, RR 0.5, 95% CI 0.2 to 1.2) or *L. acidophilus/L. bulgaricus* (1 RCT, 38 participants, RR 0.96, 95% CI 0.6 to 1.5) was not associated with a significant reduction of the risk of AAD.

The meta-analysis of 5 trials evaluating only lactic acid bacteria, after removing the trial done with *Saccharomyces boulardii,* did not change the overall result (5 RCTs, 520 participants, RR 0.5, 95% CI 0.35 to 0.7, fixed effect model; 0.5, 95% CI 0.3 to 0.9, random effect model).

As mentioned earlier, studies included in this review were undertaken using different definitions of diarrhea. The pooled effect size of 4 trials[16,17,20,23] that used similar definitions of diarrhea was 0.34, 95% CI 0.22 to 0.51. Subgroup analysis based on the type of antibiotics used was not possible, as authors of the original reports did not provide such specification.

Two RCTs[17,20] evaluated the effect of probiotics in the prevention of *C. difficile* diarrhea in children. These trials demonstrated a trend to lower risk of *C difficile* diarrhea in the probiotic group compared with the placebo group (RR 0.38, 95% CI 0.12 to1.18, fixed effect model).

Duration and severity of diarrhea

These outcome measures were either not reported in the studies included in this systematic review or were reported

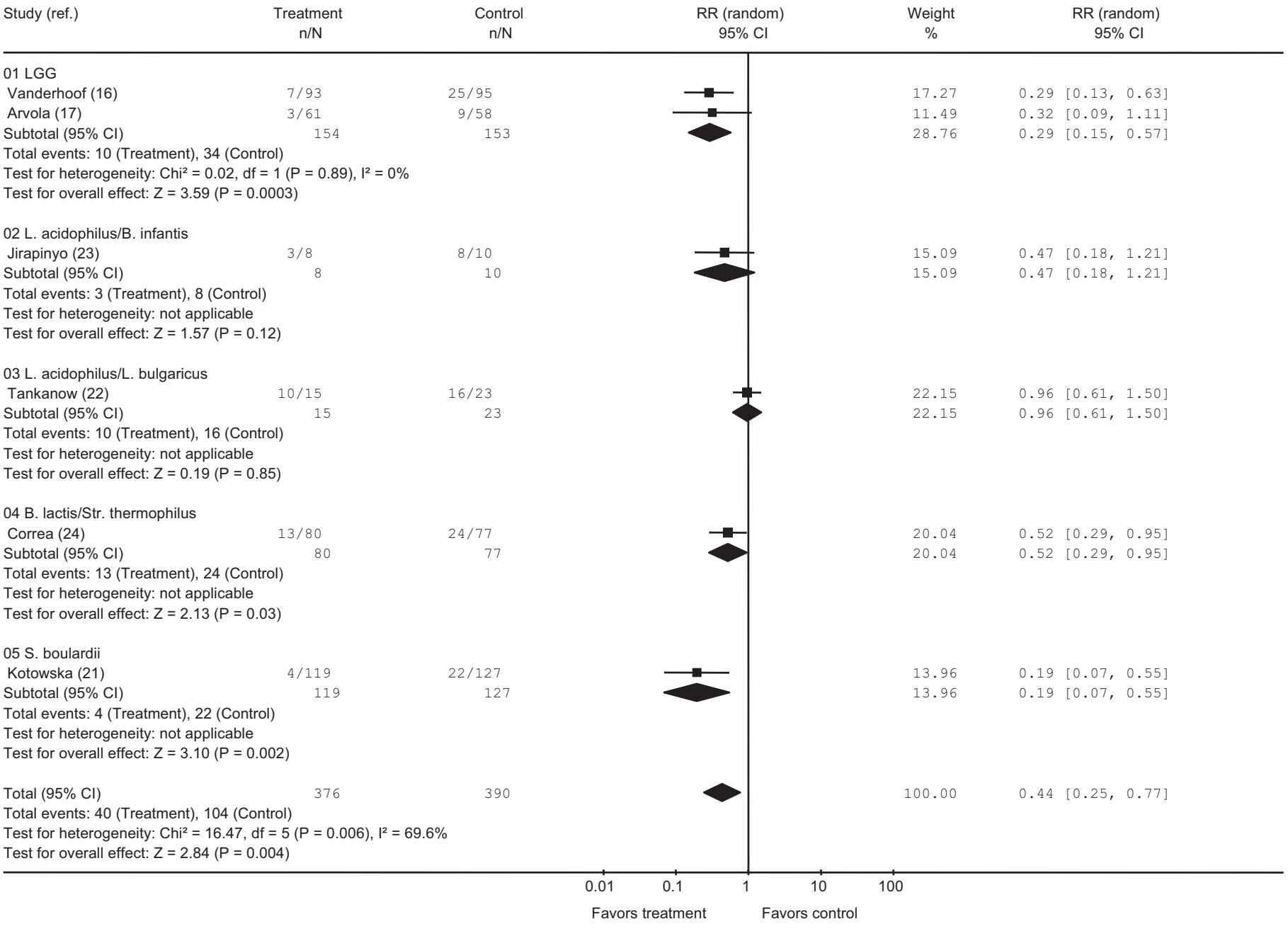

Figure. Plot of relative risk of antibiotic-associated diarrhea in children treated with probiotics compared with placebo.

in a manner that does not allow meta-analysis. Vanderhoof et al.[16] reported that the mean duration of diarrhea was 4.7 days in the intervention group compared with 5.88 days in the placebo group ($P = 0.05$). Correa et al.[23] reported no significant difference in the duration of diarrhea between groups ($P = 0.253$). Arvola et al.[17] reported that the mean duration of diarrhea was 4 days (range: 2 to 8 days); no further details were provided.

There was no need for discontinuation of antibiotic treatment, hospital treatment because of diarrhea in the outpatients, or intravenous rehydration in either of the study groups in the one trial that addressed these outcomes.[20]

DISCUSSION

Our meta-analysis finds effectiveness of probiotics in preventing AAD in children treated with antibiotics for any reason (mainly for respiratory tract infections). For every 7 patients who would develop diarrhea while being treated with antibiotics, one fewer will develop AAD if also receiving probiotics. The results of this meta-analysis confirm the findings of previous systematic reviews, which included trials comparing probiotics with placebo or no treatment for prevention of AAD.[11-14] Our meta-analysis is distinctive in that it includes only randomized controlled trials performed in children. These analyses collectively suggest that probiotics might be beneficial for AAD prevention.

Critics of using a meta-analytical approach to assess the efficacy of probiotics argue that beneficial effects of probiotics seem to be strain specific, thus, pooling data on different strains may result in misleading conclusions. In our analysis, there is evidence for preventive effects of the following probiotics in decreasing order of supporting data: *S. boulardii, Lactobacillus* GG, and the combination of *B. lactis* and *S. thermophilus.* However, as evidence is still limited, caution should be exercised until these results are confirmed by other studies. Also, the conclusions about the ineffectiveness of other probiotic strains studied are based on limited data. Further, few probiotics have been tested. Other microorganisms (e.g., *Clostridium butyricum* MIYAIRI[25]) also may be effective, although this suggestion is based on nonrandomized trials.

Our study does not allow firm conclusions regarding the efficacy of probiotics for the prevention of *C. difficile* diarrhea in children, as *C. difficile* diarrhea was not the primary outcome in any of the included trials. In adults, a recent systematic review demonstrated that available evidence does not support the administration of probiotics with antibiotics to prevent the development of *C. difficile* diarrhea and data are inadequate to justify probiotics as treatment for *C. difficile* diarrhea.[27]

It is unlikely that all antibiotics are equally selective for causing AAD. Our findings show that probiotics significantly reduce the risk of diarrhea in children treated with antibiotics in general. However, they do not allow conclusions about the efficacy of probiotics in preventing diarrhea attributable to any single antibiotic class.

Most cases of AAD are mild and self-limited, thus, do not result in cessation of antimicrobial therapy. However, cases in which antimicrobial therapy needed to be terminated were included by some authors.[21,22] Even if statistically significant, the effect of probiotics in the prevention of such symptoms may not be clinically significant. Information is needed on the efficacy of probiotics in preventing more severe cases of AAD (e.g., those leading to dehydration, cessation of treatment with antibiotics) and *Clostridium difficile* colitis. Few trials assessed the prevalence of serious complications of AAD, such as the need to terminate antibiotic treatment or hospitalize the patient for management of diarrhea or for intravenous rehydration.[20] These authors observed no such cases in children, thus, the baseline risk in the pediatric age group appears to be low.

The duration of follow-up after antibiotic treatment varied in the trials included in this meta-analysis. As diarrhea may occur up to 2 months following cessation of such treatment, some cases of AAD may have been missed.

No adverse effects due to the use of probiotics were observed in any of the included trials. However, administration of probiotics is not without risk, albeit adverse effects seem to be rare.[28] Of concern, there have been instances of fungemia associated with by *S. boulardii*[29-31] and bacteremia with certain probiotic bacteria involving high-risk populations.[32] Endocarditis, pneumonia, and meningitis have been reported in association with lactobacilli.[32-35] Most complications have occurred in immunocompromised subjects or in patients with other life-threatening illnesses managed in intensive care areas. While the use of probiotics in immunocompetent subjects seems to be safe, it is not clear whether they could be used in the prevention of AAD in immunocompromised patients.

This systematic review should be interpreted within the context of several limitations. First, systematic reviews are subject to publication bias. We took no formal steps to look for publication bias, as there were few studies on any given effect and any formal method would have had little power. Although we used an extensive search strategy for finding published trials, we did not attempt to identify unpublished trials. Second, this and any meta-analysis is limited by the quantity and quality of existing data. The methodology of the included studies differed and often was suboptimal. Potential limitations included unclear or inadequate allocation concealment, and no intention-to-treat analysis. Study limitations also included a small sample size in some trials and no widely agreed upon definition of diarrhea. Finally, all meta-analyses contain heterogeneity. The statistically significant heterogeneity among the studies makes the results of our meta-analysis less meaningful. Given the small number of studies, statistical conclusions on determinants of heterogeneity might be flawed.

Should children treated with antibiotics routinely receive probiotics? The results emerging from this meta-analysis provide evidence of a moderate beneficial effect of single probiotic microorganisms, such as *Saccharomyces boulardii* or

Lactobacillus GG, or a combination of probiotics (i.e., *Bifidobacterium lactis* and *Streptococcus thermophilus*) in the prevention of AAD. We believe that their use is warranted when prevention of this usually self-limited complication is deemed important. No reliable data on the efficacy of other probiotic strains in children are available.

The limitations discussed suggest steps to improve the quality of research in this area. Further well-conducted clinical studies using validated outcomes are recommended to: 1) further identify populations at high risk of AAD who would benefit most from probiotic therapy; 2) evaluate the efficacy of other probiotic strains; 3) evaluate the efficacy of probiotics in preventing AAD caused by *C. difficile* or associated with antibiotics that are most likely to cause diarrhea; 4) determine the most effective dosing schedule; and 5) address the cost-effectiveness of using probiotics to prevent AAD in children.

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Table I. Characteristics of the included RCTs

Trial	N (exp/cont)	Participants	Age (y)	Antibiotics	Indications	Control group	Probiotic(s)	Dose (per day)	Duration of intervention	Follow-up	Definition of diarrhea or AAD
Tankanow et al[21]	38 (15/23)	Outpatients	5 mo–6 y	Amoxicillin	Otitis media and pharyngitis	Placebo (lactose)	*L acidophilus* and *L bulgaricus*	20.4×10^8 CFU	10 d (min 5 d)	10 d (min 5 d)	≥1 abnormally loose bowel movement per day
Jirapinyo et al[22]	18 (8/10)	Inpatients	1–36 mo	Broad-spectrum antibiotics (mainly cefotaxime)	Meningitis, sepsis	Placebo (sugar)	*L acidophilus* and *B infantis*	3 capsules daily	7 d	Not stated	Not stated
Correa et al[23]	157 (87/82)	Inpatients	6–36 mo	Various (penicillin, ampicillin, oxacillin, amoxicillin, cephalosporin, amoxicillin + clavulanic acid)	Not specified	Placebo (unsupplemented formula)	Infant formula supplemented with *B lactis* 10^7 CFU and *S thermophilus* 10^6 CFU/g	*B lactis* 10^7 CFU/g and *S thermophilus* 10^6 CFU/g	15 d	30 d	≥3 liquid stools per day for at least 2 consecutive days
Arvola et al[17]	119 (61/58)	Mainly outpatients; few inpatients	2 wk–13 y	Various (penicillin, amoxicillin, cephalosporins, erythromycin, trimethoprim-sulpha)	Otitis, tonsillitis, and respiratory tract infections	Placebo (microcrystalline cellulose)	*Lactobacillus* GG	2×10^{10} CFU; twice daily	7–10 d	14 d (entire 3 months)	≥3 liquid or loose stools/24 h on ≥2 d
Vanderhoof et al.[16]	188 (93/95)	Outpatients	6 mo–10 y	Various (amoxicillin, amoxicillin/clavulanate, cefprozil, clarithromycin)	Respiratory tract infections, dermatologic	Placebo (insulin)	*Lactobacillus* GG	1×10^{10} CFU to 2×10^{10} CFU once daily	10 days	Duration of antibiotic treatment or diarrhea ceased	≥2 liquid stools/24 h on ≥2 d
Kotowska et al[20]	246 (119/127)	Outpatients and inpatients	6 mo–14 y	Various (cefuroxime axetil, amoxicillin + clavulanate, amoxicillin, cefuroxime, roxithromycin)	Otitis media and/or respiratory tract infections	Placebo (lactose)	*Saccharomyces boulardii*	500 mg	For the duration of antibiotic treatment (experimental group 7.8 ± 1 d; control group 8.1 ± 1 d)	Duration of antibiotic treatment + 2 wk	Diarrhea; ≥3 loose or watery stools per day for a min of 48 h during and/or up to 2 wk after the end of antibiotic treatment AAD: As above, caused by C difficile or for otherwise unexplained diarrhea

CFU, colony forming units.