Probiotics in the prevention of antibiotic-associated diarrhea in children: a meta-analysis of randomized controlled trials
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CRD summary
This review concluded that probiotics (live microbial supplements) significantly reduce the risk of diarrhoea in children treated with antibiotics. The authors’ conclusions are in line with the evidence presented and appear reliable, although the quantity and quality of evidence for the effectiveness of specific probiotics in particular populations and settings is limited.

Authors' objectives
To evaluate the effectiveness of probiotics in preventing antibiotic-associated diarrhoea (AAD) in children.

Searching
The authors searched MEDLINE, EMBASE and CINAHL from inception to December 2005, the Cochrane Database of Systematic Reviews (Issue 2, 2005) and the Cochrane CENTRAL Register (Issue 4, 2005); the search terms were reported. No language restrictions were imposed. The reference lists of relevant studies and reviews were also screened.

Study selection
Randomised controlled trials (RCTs) comparing probiotics with placebo or no intervention in children who had received antibiotics for any reason in any setting were eligible for inclusion. The primary outcomes of the review were the incidence of diarrhoea or AAD (as defined by the investigator) and incidence of *Clostridium difficile*-associated diarrhoea. The secondary outcomes were mean duration of diarrhoea, need to discontinue antibiotic treatment, hospitalisation, intravenous rehydration and adverse events. The included studies varied in sample size, setting, age of the participants, probiotic used and dose, and antibiotics administered. All of the included studies were placebo-controlled.

Two reviewers independently selected studies for inclusion and any disagreements were resolved by discussion.

Assessment of study quality
Validity was assessed on the basis of allocation concealment, blinding, intention-to-treat analysis and loss to follow-up. Risk of bias was classified as low (up to one inadequate item), medium (up to three inadequate items), high (more than three inadequate items) or very high (no description of methods).

The authors did not state how the validity assessment was performed.

Data extraction
For dichotomous outcomes, data on the number of events in each group were used to calculate the relative risk (RR) and 95% confidence interval (CI) for each study.

Two reviewers independently extracted the data using standard forms and any discrepancies were resolved by discussion.

Methods of synthesis
The studies were combined by meta-analysis using either fixed-effect or random-effects models. Study weighting was based on the inverse of the variance. Statistical heterogeneity was assessed using the Cochran Q statistic (p<0.05 considered significant) and I² statistic. Predefined subgroup analyses investigated the influence of probiotic strain, definition of diarrhoea and type of antibiotic on the magnitude of the treatment effect. Sensitivity analyses were performed to assess the effects of study quality.
Results of the review
Six RCTs with 766 participants were included.

Risk of bias was rated low for 2 studies, medium for 3 studies and high for 1 study.

Across all studies, probiotic treatment significantly reduced the risk of diarrhoea (random-effects RR 0.44, 95% CI: 0.25, 0.77). Statistical heterogeneity was significant (p=0.006), but the exclusion of the study with high risk of bias gave a significant estimate of effect (fixed-effect RR 0.35, 95% CI: 0.24, 0.51) without significant heterogeneity. Probiotics *Lactobacillus rhamnosus* GG (2 RCTs), *Saccharomyces boulardii* (1 RCT), and *B. lactis* and *Streptococcus thermophilus* (1 RCT) significantly reduced the risk of AAD, while *L. acidophilus*/*Bifidobacterium infantis* (1 RCT) or *L. acidophilus*/*L. bulgaricus* (1 RCT) did not. There was no significant effect of probiotic therapy on *Clostridium difficile* diarrhoea (RR 0.38, 95% CI: 0.12, 1.18; 2 RCTs). Other analyses were reported.

One RCT reported a shorter duration of diarrhoea in the probiotic group while another reported no significant difference. There were no cases of antibiotic discontinuation, hospitalisation of out-patients, or intravenous rehydration in either study group in the only RCT that reported these outcomes.

Authors' conclusions
Probiotics significantly reduce the risk of AAD in children.

CRD commentary
This review addressed a clear question and had clear inclusion criteria. The authors searched a reasonable range of sources without applying language restrictions. Unpublished studies were not sought, so the review may be at risk of publication bias. Validity was assessed using standard criteria and the results were used in the analysis. Measures were taken to reduce the risk of error and bias during the review process, although the methods used to assess validity were not reported. Relevant details of the included studies were presented in the text and tables available online. The studies were combined by meta-analysis. Significant heterogeneity was found for the primary outcome but this was accounted for by the presence of one study with a high risk of bias. The authors' conclusions are in line with the evidence presented and appear reliable, although the quantity and quality of evidence for the effectiveness of specific probiotics in particular populations and settings is limited.

Implications of the review for practice and research
Practice: The authors stated that the use of probiotics is warranted when the prevention of AAD is deemed important.

Research: The authors stated that further research is needed to identify populations who would benefit most from probiotic therapy; to evaluate other probiotic strains; to evaluate probiotics for the prevention of AAD caused by *Clostridium difficile*, or associated with antibiotics most likely to cause diarrhoea; to evaluate probiotic effectiveness in reducing the frequency of severe AAD; to determine the most effective dosing schedule; and to assess the cost-effectiveness of probiotic therapy.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.