Authors' objectives
To perform a meta-analysis of published trials on the efficacy of probiotics in reducing the incidence of antibiotic-associated diarrhoea.

Searching
The authors conducted electronic searches of MEDLINE and Cochrane registers, and manual searches of abstract books of all major gastroenterology congresses and meetings over the previous 15 years, for studies performed between 1966 and 2001. The search terms for the electronic searches were listed. The search was limited to randomised studies, but was not restricted by language. Personal unpublished data from authors and international experts were also sought.

Study selection
Study designs of evaluations included in the review
Placebo-controlled trials were eligible for inclusion.

Specific interventions included in the review
Studies in which a single probiotic species was administered were eligible for inclusion. The included trials assessed the decrease in the occurrence of antibiotic-associated diarrhoea during the administration of Saccharomyces boulardii (3 trials) and Lactobacillus spp. (4 trials).

Participants included in the review
The authors did not specify any inclusion criteria relating to the participants. The included trials included paediatric populations (2 trials), elderly populations (1 trial) and adults (4 trials).

Outcomes assessed in the review
Studies that considered diarrhoea as the primary end point, with a minimum follow-up of 2 weeks, were eligible for inclusion.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The trials were assessed according to the quality criteria published by Nicolucci et al. (see Other Publications of Related Interest). Two investigators, who did not take part in any of the trials initially selected, independently evaluated the quality of the trials. It was not stated whether the level of agreement was assessed or how any disagreements were resolved. Studies with serious design flaws, such as an unclear definition of end point or ambiguous treatment scheme, were excluded from the review.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. Data were extracted on the number and age of the participants, the type of antibiotic used, probiotic species used, duration of therapy, definition of diarrhoea and parallel laboratory testing.

Where available, raw data from the authors of single studies were used. Data based on the presence or absence of diarrhoea were included, but not results based on differences in the amount of daily stool discharge. Treatment efficacy was evaluated from a per protocol analysis.
Methods of synthesis
How were the studies combined?
Due to differences in the methods and scales used to measure diarrhoea, the occurrence of antibiotic-associated diarrhoea was assessed as a binomial variable. A combined relative risk (RR) among studies was calculated according to the Mantel-Haenszel method. Confidence intervals (CIs) were calculated using the Cornifield formula. The level of significance for the determination of a beneficial effect of probiotic treatment on diarrhoea was a combined RR and CI of lower than 1.0.

Publication bias was assessed using a funnel plot.

How were differences between studies investigated?
Homogeneity was assessed using the Mantel-Haenszel test. Homogeneity was considered to be significant when the P-value was less than 0.05, according to a chi-squared data distribution.

Results of the review
Seven placebo-controlled trials, with a total of 881 participants, met the inclusion criteria.

Compared with placebo, probiotic supplements were associated with a statistically-significant decrease in the incidence of antibiotic-associated diarrhoea. The Mantel-Haenszel combined RR was 0.3966 (95% CI: 0.275, 0.571). The RRs for three of the individual studies, two of which contained the highest numbers of participants, were also significant.

Homogeneity was not statistically significant (chi-squared=6.001, d.f.=6, P=0.42). The funnel plot of study odds ratios versus sample sizes was symmetrical, thus suggesting there was no study selection bias present.

Authors’ conclusions
The results suggested a strong benefit of probiotic administration on antibiotic-associated diarrhoea, but further data are needed. The evidence for beneficial effects is still not definitive. Published studies were flawed by the lack of a placebo design.

CRD commentary
The review was based on a well-defined question, with clearly stated inclusion criteria relating to the study design, intervention and outcomes of interest. However, the authors did not specify inclusion criteria relating to the participants in the trials; this resulted in different study populations in relation to age, geographical area and socioeconomic background. The authors searched only two electronic databases, although they also actively searched for unpublished studies and did not restrict their search by language of publication. The electronic search terms were listed. A funnel plot was used and this did not indicate the presence of study selection bias.

Two investigators independently evaluated the quality of the trials using a published checklist. However, the authors did not provide details of the study selection or data extraction processes, which could allow the introduction of errors and reviewer bias. Adequate data on the individual trials were presented in tabular format and in the text.

There was statistically-significant heterogeneity between the studies, which makes the results of the meta-analysis less meaningful. However, the authors reported that the RRs for three of the individual studies, including two studies with a large number of participants, were also statistically significant.

Overall, the review appears to have been well conducted and reported, and the authors’ conclusions are supported.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that general practice, worldwide, large-scale, multicentre, prospective data on the primary prevention of antibiotic-associated diarrhoea should be obtained. The lack of standardisation of the probiotic
preparations used calls for more equivalent formulations. A cost-benefit analysis should be undertaken in future investigations.

Bibliographic details

PubMedID
12182746

Other publications of related interest

Indexing Status
Subject indexing assigned by NLM

MeSH
Acute Disease; Adult; Aged; Anti-Bacterial Agents /adverse effects; Antidiarrheals /therapeutic use; Diarrhea /chemically induced /prevention & control; Humans; Middle Aged; Probiotics /therapeutic use; Randomized Controlled Trials as Topic

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Record Status
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.