Probiotics in the treatment and prevention of acute infectious diarrhea in infants and children: a systematic review of published randomized, double-blind, placebo-controlled trials

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Authors' objectives
The authors aimed to determine the effect of probiotics in the treatment and prevention of acute infectious diarrhoea in infants and children.

Searching
MEDLINE (from 1966 to April 2001) and the Cochrane Controlled Trials Register (April 2001) were searched; the search terms were stated. The authors also searched for reports published by experts in the field, and checked the reference lists in identified studies, reviews and book chapters. Pharmaceutical industry files prepared by the manufacturers of probiotics were handsearched. Non-English language reports were translated. Unpublished reports and abstracts were excluded.

Study selection
Study designs of evaluations included in the review
Double-blind randomised controlled trials (RCTs) were eligible for inclusion. Pseudo-randomised trials were excluded.

Specific interventions included in the review
Studies that compared probiotics with placebo as prevention or treatment were eligible for inclusion. Studies that did not include a placebo control treatment were excluded. The treatment studies used the following probiotic strains: Lactobacillus strain GG (LGG), L. reuteri, L. acidophilus LB, Saccharomyces boulardii, Streptococcus thermophilus lactis, L. acidophilus and L. bulgaricus. The prevention studies evaluated either LGG, or a combined preparation of Streptococcus thermophilus and Bifidobacterium bifidum.

Participants included in the review
Studies of infants and children with acute diarrhoea were eligible for inclusion. Acute diarrhoea was defined as more than three loose or watery stools within a 24-hour period, with the diarrhoea lasting less than 7 days. Studies of diarrhoea induced by antibiotics were excluded. The included studies were of children aged 1 to 48 months. The treatment studies were predominantly of hospitalised children in developed countries. Diarrhoea in the treatment studies was bacterial, due to human rotavirus, or of undetermined origin. The prevention studies were of hospitalised children in developed countries and children in the community, including undernourished children. Diarrhoea in these studies was nosocomial or community acquired.

Outcomes assessed in the review
Studies that assessed any patient outcome were eligible for inclusion. The primary outcomes assessed in the review were the total duration of diarrhoea (treatment studies) and the incidence rate of diarrhoea on the third day (prevention studies). The duration of diarrhoea (treatment studies) and adverse effects (all studies) were also assessed.

How were decisions on the relevance of primary studies made?
One reviewer excluded irrelevant citations. Two reviewers then independently selected trials using the full-text reports and resolved any disagreements by discussion. The reviewers were not blinded to the authors, journals, results, or conclusions of the individual studies. Inter-reviewer agreement on study selection was measured using weighted kappa statistics.

Assessment of study quality
Validity was assessed and scored using the Jadad scale, which considers randomisation, blinding and withdrawals (see Database of Abstracts of Reviews of Effects (DARE) Produced by the Centre for Reviews and Dissemination Copyright © 2015 University of York
Other Publications of Related Interest). Two reviewers independently assessed validity and resolved any disagreements by discussion. Inter-reviewer agreement on study quality was measured using weighted kappa statistics.

**Data extraction**

One reviewer extracted the data using a standardised form and a second reviewer checked the extraction. Information on the following was tabulated: country of study; study setting for prevention studies; inclusion and exclusion criteria; age range of participants; probiotic strain and dose; intervention regimen; outcomes assessed; and aetiology or type of diarrhoea.

Risk ratios (RR) and 95% confidence intervals (CIs) between the intervention and placebo groups were calculated for the presence of diarrhoea on day 3 for each study.

**Methods of synthesis**

How were the studies combined?

The pooled RR (and 95% CI) between probiotics and placebo was calculated for the presence of diarrhoea on day 3 using fixed-effect and random-effects models. The pooled weighted mean difference (WMD) of the duration of diarrhoea between probiotics and placebo was calculated, along with the 95% CI, with weighting based on the inverse of the variance. The number-needed-to-treat (NNT) was calculated, along with the 95% CI. The data were expressed as patient-months and incidence rate of diarrhoea cases per patient-months in the probiotic and placebo groups, and the incidence rate ratio of diarrhoea was then estimated.

How were differences between studies investigated?

Statistical heterogeneity was assessed using the chi-squared statistic. Subgroup analyses were used to explore the influence of the type of probiotic and the aetiology of the diarrhoea (viral versus bacterial). A sensitivity analysis was used to explore potential sources of significant heterogeneity.

**Results of the review**

Ten RCTs (at least 733 children) of treatment and 3 RCTs of prevention (340 children) were included.

Inter-rater agreement on study selection and study quality was good (kappa 0.72 for selection and 0.78 for quality). The quality scores ranged from 3 to 5 (median 4) out of a potential 5 points.

**Treatment of diarrhoea.**

Compared with placebo, probiotics significantly reduced the risk of diarrhoea lasting more than 3 days; the RR (8 RCTs, 731 children) was 0.43 (95% CI: 0.34, 0.53) with the fixed-effect model. No significant heterogeneity was detected (P=0.12). In terms of the influence of the probiotic strain, only LGG consistently significantly reduced the risk of diarrhoea lasting more than 3 days; the RR (3 RCTs, 397 children) was 0.49 (95% CI: 0.36, 0.66) with the fixed-effect model. The NNT with LGG to avoid one case of diarrhoea lasting more than 3 days was 4 (95% CI: 3, 9) when using a conservative random-effects model. The NNT for Saccharomyces boulardii (1 RCT) was 2 (95% CI: 2, 3). It was not possible to explore the influence of aetiology of diarrhoea due to the lack of appropriate data.

Compared with placebo, probiotics significantly reduced the duration of diarrhoea; the pooled WMD (8 RCTs, 733 children) was -18.2 hours (95% CI: -26.9, -9.5) with the random-effects model. Significant heterogeneity was detected (P=0.015). Heterogeneity appeared to be due to one RCT reporting no significant difference between unspecified strains of Streptococcus thermophilus, L. acidophilus, and L. bulgaricus and placebo. Excluding this RCT resulted in homogeneity. A meta-analysis of 4 RCTs (297 children with, predominantly, confirmed rotavirus diarrhoea) found that probiotics (LGG and L. reuteri) significantly reduced the duration of diarrhoea compared with placebo; the pooled WMD was -24.8 hours (95% CI: -31.8, -17.9, P<0.001). No significant heterogeneity was detected (P=0.82). A subset analysis of 53 children with invasive enteric infections from one RCT found no significant difference between probiotics and placebo; the WMD was 1.3 hours (95% CI: -15.3, 17.9).

**Prevention of diarrhoea.**
Clinical and statistical heterogeneity (P=0.007) precluded meta-analysis. The 3 RCTs varied in terms of the inclusion criteria, setting, type of diarrhoea, intervention regimen, exposure to human rotavirus and outcome measures. Only one of the 3 RCTs found that probiotics significantly reduced the incidence of diarrhoea; the other two found no significant difference between treatments.

Adverse effects.

No adverse effects were reported.

Authors’ conclusions
Probiotics significantly reduced the duration of acute infectious diarrhoea in infants and children, especially diarrhoea due to rotavirus. No conclusions could be reached about the use of probiotics in the prevention of diarrhoea due to clinical and statistical heterogeneity among the studies.

CRD commentary
The review question was clear in terms of the study design, intervention and participants. The inclusion criteria were not explicitly defined in terms of the outcomes, but the outcomes assessed in the review were stated clearly. Restricting the search two databases may, as the authors correctly acknowledged, have resulted in the omission of other relevant studies. The search terms were stated and studies published in any language were eligible for inclusion. However, no attempt was made to locate unpublished studies, thus raising the possibility of publication bias. Only one reviewer excluded irrelevant citations, but two reviewers independently selected studies from full-text reports, assessed validity and extracted the data; this reduces the potential for bias and errors. Validity was assessed using validated criteria, and inter-rater agreement was estimated for the study selection and validity assessment processes.

Relevant information on the included studies was tabulated. Data for the treatment studies were combined appropriately in a meta-analysis and statistical heterogeneity was assessed. Potential sources of heterogeneity for these studies were explored. The authors correctly considered that the clinical and statistical heterogeneity among the prevention studies precluded meta-analysis. It was unclear whether the RCTs reported that no adverse effects occurred, or whether the adverse effects were not reported in the included studies. The evidence presented appears to support the authors’ conclusions.

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

Research: The authors stated that further double-blind placebo-controlled RCTs, which assess carefully selected and defined strains of probiotics and use standardised outcomes including stool output, are required.

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