Role of Lactobacillus in the prevention of antibiotic-associated diarrhea: a meta-analysis
Kale-Pradhan PB, Jassal HK, Wilhelm SM

CRD summary
This review concluded that a prophylactic Lactobacillus single-agent regimen, administered during antibiotic treatment, appeared to reduce the risk of developing antibiotic-associated diarrhoea compared with placebo. The author's conclusions are suitably cautious, but need to be considered against the variation in the evidence and possible language and publication bias.

Authors' objectives
To evaluate the efficacy of a Lactobacillus probiotic single-agent regimen for preventing antibiotic-associated diarrhoea.

Searching
PubMed, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL) and the Cochrane Database of Systematic Reviews were searched from inception to May 2008. Search terms were reported. The search was restricted to papers published in English. Reference lists of reviews were also handsearched.

Study selection
Randomised, placebo-controlled, blinded clinical trials of a Lactobacillus single-agent regimen for antibiotic-associated diarrhoea prevention in adults or paediatrics were eligible for inclusion. Eligible trials had to report on the frequency of antibiotic-associated diarrhoea. Trials of Lactobacillus combination regimens were excluded.

Included trials were in adult or paediatric inpatient or outpatient populations. Participant ages ranged from two weeks to 14 years (paediatric) and from 18 to 93 years (adults); the total proportion of males was 50.4%, where reported. Lactobacillus doses and regimens varied from \(2 \times 10^9\) to \(4 \times 10^{10}\) colony-forming units per day (CFU/day), given as capsules twice a day to sachets four times a day. Treatment was given for between three and 14 days. Trial follow-up periods ranged from two days to three months after completion of the probiotic regimen.

Studies were selected by two reviewers independently, with discrepancies resolved by consensus.

Assessment of study quality
The Jadad scale was used to assess validity including randomisation methods; allocation concealment; and reporting of withdrawals and drop-outs (scored from 0 to 5 points).

Validity assessment was performed by two reviewers independently, with discrepancies resolved by consensus.

Data extraction
Results for the occurrence of antibiotic-associated diarrhoea and adverse events were extracted and used to calculate risk ratios (RR) with 95% confidence intervals (CI).

Data were extracted by two reviewers independently, with discrepancies resolved by consensus.

Methods of synthesis
Results were pooled used a random-effects meta-analysis. Statistical heterogeneity was measured using the \(I^2\) statistic. A funnel plot was used to evaluate publication bias.

Results of the review
Ten randomised controlled trials (RCTs) were included in the review (n=1,862 participants); four paediatrics RCTs (n=585 participants) and six adults RCTs (n=1,277 participants). Jadad scores ranged from 2 to 5.
Treatment with *Lactobacillus* probiotic reduced the risk of developing antibiotic-associated diarrhoea compared with placebo (RR 0.35, 95% CI 0.19 to 0.67; heterogeneity $I^2$=79%). Subgroup analyses of the adult and paediatric populations found a similar risk reduction for adults (RR 0.24, 95% CI 0.08 to 0.75; heterogeneity $I^2$=83%), but no difference between groups for the paediatric population. The funnel plot was asymmetric, indicating possible publication bias.

Five RCTs reported on adverse events; three of these reported no statistically significant difference between groups. One trial reported more diarrhoea and taste disturbance in the placebo group compared with the *Lactobacillus* group (diarrhoea 30% versus 5%, $p=0.0018$; taste disturbance 40% versus 9.5%, $p=0.0027$). Another trial also reported more diarrhoea (26.6% versus 3.3%) and taste disturbance (50% versus 23.3%), as well as an increase in nausea (36.6% versus 10%), in the placebo group.

**Authors' conclusions**

A prophylactic *Lactobacillus* single-agent regimen, administered during antibiotic treatment, appeared to reduce the risk of developing antibiotic-associated diarrhoea compared with placebo.

**CRD commentary**

This review had clearly stated study inclusion criteria and conducted a good literature search. All review methods (searching, study selection, data extraction and validity assessment) were performed by two people independently, and the general conduct and reporting of this review was good. The main drawbacks were the restriction to trials published in English, the lack of a full report of the quality of each trial, and pooling trials that appeared to have very heterogeneous results. The authors did assess publication bias and found some evidence for it, probably partially due to the bias caused by the language restriction. There was no investigation of possible reasons for the heterogeneity and, although the random-effects analysis was the more appropriate, sensitivity analyses would have been helpful.

The author's conclusions are suitably cautious, but need to be considered against the heterogeneity of the evidence and possible language and publication bias.

**Implications of the review for practice and research**

**Practice:** The authors stated that *Lactobacillus* may be a feasible option for preventing antibiotic-associated diarrhoea.

**Research:** The authors stated that further evaluations with standardised *Lactobacillus* doses and regimens that include sample size calculations and recruit enough patients, are needed.

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