CRD summary
The authors concluded that high doses of probiotic preparations that contained several different strains of probiotics seemed more effective at preventing diarrhoea than single-strain probiotics. However, the small number of available studies precluded any firm conclusions and further research was needed. Given the small number and limited quality of available studies and the presence of significant statistical heterogeneity, the authors’ caution is justified.

Authors’ objectives
To evaluate the effectiveness of probiotics for prevention and treatment of radiation-induced diarrhoea.

Searching
PubMed, EMBASE, The Cochrane Library, Google Scholar, Cochrane Central Register of Controlled Trials (CENTRAL), meta Register of Controlled Trials and National Institutes of Health databases and websites were searched up to January 2009 for articles in any language. Search terms were reported. Bibliographies of retrieved articles were handsearched. Abstracts from three relevant meetings were handsearched until 2008. Published and unpublished articles were eligible for inclusion.

Study selection
Randomised controlled trials (RCT) with at least two parallel groups that evaluating probiotic supplementation for treatment or prevention of radiation-induced diarrhoea were eligible for inclusion.

Included studies were of Lactobacillus casei, Lactobacillus acidophilus, Lactobacillus rhamnosus or VSL no 3 in varying doses, administered compared to placebo or restricted diet. In most studies, probiotics were administered preventatively. One study was of therapeutic probiotic treatment. Included patients received postoperative radiotherapy. Doses ranged from 45Gy to 80Gy. In one study, patients also underwent intracavitary preoperative caesium. In another study some patients also received concomitant cisplatin 40mg/m². Included patients had tumours of the endometrial adenocarcinoma, cervical, sigmoid, rectal, uterine, ovarian or prostate, or other lower abdomen tumours. One study was of women only. Outcomes included for the review were development of diarrhoea, severity of diarrhoea, use of anti-diarrhoeal medication, number of bowel movements, change in stool consistency, time before development of diarrhoea, time before change in stool consistence, quality of life score, safety profile and patients' rating of diarrhoea.

Two reviewers independently selected studies for the review. Disagreements were resolved by consensus.

Assessment of study quality
Methodological quality of the included trials was assessed according to criteria by Juni et al. (2001), which included randomisation, allocation concealment, blinding, description of follow-up, control group, definition of outcome measures, definition of a responder, adequate power, intention-to-treat analysis, definition of treatment regimens and comparability of groups at baseline. Two reviewers independently evaluated the quality of the included studies.

Data extraction
The number of patients who developed diarrhoea in each group was extracted and used to calculate odds ratios (OR) with 95% confidence intervals (CI). Both per-protocol and intention-to-treat results were extracted. Two reviewers independently extracted data for the review.

Methods of synthesis
For the outcome of non-response to treatment in the preventative studies, pooled ORs with 95% CIs were calculated using a random-effects model on an intention-to-treat basis. Statistical heterogeneity was assessed using the Q-test and Higgins' test. Publication bias was not assessed due to the small number of trials. The studies were combined in a narrative synthesis.
Results of the review
Four randomised placebo-controlled trials (RCTs) were included for the review (n=837). Three studies were double-blinded. Allocation concealment was adequate in one trial and unclear in three trials. Withdrawals and dropouts were adequately explained in all studies. Only one study performed an intention-to-treat analysis. No studies were adequately powered.

Prevention (three studies, n=632): When the studies were combined in a meta-analysis, probiotic supplementation did not significantly decrease the risk of developing diarrhoea compared to placebo (OR 0.47, 95% CI: 0.13 to 1.67). There was evidence of significant statistical heterogeneity. One RCT (n=24) found that *Lactobacillus acidophilus* use significantly reduced the incidence of diarrhoea (27% versus 90%, p<0.001) and need for medication (9% versus 60%, p<0.01) compared to a restricted diet. One RCT (n=490) found that incidence and severity of diarrhoea was significantly less in participants who took VSL compared to placebo (p<0.001). One RCT (n=118) found no significant differences between participants who took *Lactobacillus casei* and the placebo group.

Treatment (one study, n=205): One RCT of participants with diarrhoea symptoms starting within four weeks of radiation therapy found no significant differences between participants who received *Lactobacillus rhamnosus* and those who received placebo.

No major adverse events were reported.

Authors’ conclusions
High doses of probiotic preparations that contained several different strains of probiotics seemed to be more effective at preventing diarrhoea than single-strain probiotics. However, the small number of available studies precluded any firm conclusions and further research was needed.

CRD commentary
The review addressed a clear question with well-defined inclusion criteria. Several relevant databases were searched and appropriate steps were taken to minimise the risk of publication and language biases. Suitable measures were taken to minimise risks of reviewer error and bias. Methodological quality of the included studies was assessed using relevant criteria. The methodological quality of included studies was moderate; all studies were underpowered. Suitable methods were used to combine the studies. However, there was evidence of significant statistical heterogeneity that was not explored. Given the small number and limited quality of available studies and the presence of significant statistical heterogeneity, the authors’ caution is justified.

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

Research: The authors stated that further methodologically rigorous, randomised, placebo-controlled or head-to-head comparisons were needed to determine the efficacy of probiotic supplementations in prevention and treatment of radiation-induced diarrhoea.

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