Probiotic supplementation during pregnancy or infancy for the prevention of asthma and wheeze: systematic review and meta-analysis

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CRD summary
This review concluded that there was no evidence to support perinatal probiotics to prevent doctor-diagnosed asthma or childhood wheeze. These conclusions reflect the evidence presented and are likely to be reliable.

Authors' objectives
To assess the effects of probiotics during pregnancy or infancy for the prevention of asthma and wheeze in infants.

Searching
MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched for relevant published articles included up to August 2013. Search terms were available in an online appendix. The ICTRP and the conference proceedings of five relevant organisations, for the previous five years, were searched. Forward searches were performed, in Web of Science, for all included studies and relevant reviews. Reference lists of reviews and included studies were examined.

Study selection
Randomised controlled trials (RCTs) evaluating any prenatal or postnatal administration of probiotics to mother or infant were eligible for inclusion. Over 80% of infants in each trial had to be under one year old, or unborn, and to be healthy (not suffering from acute illness) at randomisation. Trials of infants with allergic disorders (other than wheeze or asthma) were eligible. Where most infants were preterm (<36 weeks gestation), trials were excluded. Comparators could be active (non-probiotic), no intervention, or placebo. The primary outcome was the incidence of doctor-diagnosed asthma. Secondary outcomes were the incidences of parent-reported asthma, wheeze (and recurrence), asthma medication, hospital admission for asthma, and lower respiratory tract infection, and the Asthma Predictive Index Score. Safety outcomes were severe gastrointestinal disturbances, allergic reaction to probiotic, and withdrawal due to perceived side-effects.

In the included trials, the probiotic organism, daily dose, and timing varied; probiotics were oral in various forms (details reported). Interventions lasted from one to 25 months. Some trials evaluated combinations of organisms or probiotics with prebiotics. Most trials were conducted in Europe (two in the UK), with the remaining trials conducted in Australia, New Zealand or Taiwan. Most trials were of infants at a high risk of asthma; the others were of general populations. Most trials did not restrict feeding practices; some required exclusive formula feeding at enrolment. Infant age at the last follow-up ranged from four months to eight years. Caesarean delivery incidence ranged from zero to 45%, where reported.

Two reviewers independently selected trials for inclusion. Disagreements were resolved through discussion with a third reviewer.

Assessment of study quality
Trial quality was assessed using the Cochrane risk of bias tool. Trial authors were contacted for clarification, where necessary.

Two reviewers independently assessed quality.

Data extraction
The data were extracted for the relevant outcomes and used to calculate risk ratios with 95% confidence intervals, for predefined time periods (age under three years, three to under six years, and six years or older). Peto odds ratios (for rare outcomes) were calculated. Where a trial reported more than one time point, the results from the longest follow-up (intention to treat) were used; the results from earlier time points were included in subgroup analyses. Trial authors were contacted for additional data where necessary.
Two reviewers independently extracted the data. Disagreements were resolved through discussion with a third reviewer.

**Methods of synthesis**

Pooled risk ratios and 95% confidence intervals were calculated using a Mantel-Haenszel random-effects model, and Peto odds ratios were calculated using a fixed-effect model. Statistical heterogeneity was assessed using $I^2$.

Subgroup analyses were conducted to estimate the effects for: participants receiving intervention (mother or infant), duration and timing of intervention (prenatal or postnatal), probiotic organism and dose, duration of follow-up or age at assessment, asthma risk, caesarean delivery rate, geographical area, and source of funding. A meta regression was used to evaluate the differences in effects, according to duration of follow-up, as a continuous variable.

**Results of the review**

Twenty RCTs (4,866 infants) were included. Most RCTs were judged to be of unclear (nine RCTs), or high (10 RCTs) risk of bias; one was at a low risk of bias. Bias was mainly due to attrition. Follow-up ranged from four months to eight years.

There were no significant differences between children receiving probiotics and those receiving placebo, for the incidence of asthma at final assessment (RR 0.99, 95% CI 0.81 to 1.21; nine RCTs; $I^2=0$). The results were similar for the Peto odds ratio for rare events (data not reported).

There were no significant differences between probiotics and placebo at final assessment for the incidence of wheeze (nine RCTs, $I^2=0$), and lower respiratory tract infections (six RCTs; $I^2=0$), but the authors noted that the increases could be clinically relevant. Four of the six trials reporting lower respiratory tract infections documented them as adverse events, when these trials were removed from the analysis, there were still no significant differences between groups. Mixed results were reported for recurrent wheeze (three RCTs; $I^2=83$%)

Most trials did not report severe gastrointestinal disturbances and allergic reactions. There were no significant differences between probiotic and control groups for withdrawal due to perceived side-effects (eight RCTs; $I^2=0$).

The results of the subgroup analyses were similar to the overall results.

**Authors' conclusions**

There was no evidence to support perinatal probiotics to prevent doctor-diagnosed asthma or childhood wheeze.

**CRD commentary**

The review question and inclusion criteria were clearly defined. Various relevant sources were searched. Appropriate methods to reduce reviewer error and bias were used throughout the review. Trial quality was assessed, using published criteria, and the results were reported. All trials were described as double-blind, but this was not supported by the quality results, where four trials had a high or unclear risk of bias for blinding.

The authors acknowledged that most of the trials were industry supported. The methods of analysis appear to have been appropriate. Statistical heterogeneity was assessed and was absent from most analyses. Some limitations were noted by the authors, such as the pooling of data from trials conducted in selected populations (infants at a high risk of asthma) and with differing probiotic formulations at various doses.

The authors’ conclusions reflect the evidence presented and are likely to be reliable.

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

**Practice:** The authors stated that the RCTs had not yielded sufficient evidence to recommend probiotics for the primary prevention of asthma or childhood wheeze.

**Research:** The authors stated a number of recommendations including the need for extended follow-up of existing trials, with further clinical and basic research, to accurately define the role of probiotics in the prevention of childhood asthma. Research was recommended to explore any association between probiotics and an increased risk of lower respiratory tract infection.
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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.