Does antibiotic exposure during infancy lead to development of asthma: a systematic review and metaanalysis

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CRD summary
The review assessed the association between taking antibiotics in the first year of life and the subsequent development of asthma in children. The authors concluded that taking antibiotics in infancy appeared to increase the risk of children developing asthma. The evidence was not strong enough to support a firm conclusion.

Authors' objectives
The overall objective was to determine the association between exposure to antibiotics in the first year of life and the development of childhood asthma.

Searching
MEDLINE, EMBASE, EBM Reviews (containing: ACP Journal Club, the Cochrane Controlled Trials Register, the Cochrane Database of Systematic Reviews and DARE), Web of Science, PapersFirst and ProceedingsFirst were searched. The period covered was 1966 to 2004. The search terms (MeSH) were reported. The reference lists in articles selected for inclusion were checked for additional studies. There was no language restrictions for the search but only studies published in English were eligible for inclusion.

Study selection
Study designs of evaluations included in the review
It was implicit that observational studies were eligible for inclusion. Prospective and retrospective studies were included (the actual design of the studies was not fully reported).

Specific interventions included in the review
Studies that assessed antibiotic exposure, defined as receipt of at least one prescription for an antibiotic in the first year of life, were eligible for inclusion. Details of the actual antibiotic exposure in the included studies were not reported. All but one of the included studies provided data for the analysis of at least one antibiotic exposure; 5 studies provided data on more than one course of antibiotics.

Participants included in the review
Studies in infants who had been exposed to the intervention in the first year of life and in whom the outcome was assessed between 1 and 18 years of age were eligible for inclusion. The participants in the included studies were identified from general population sources (primary schools, health maintenance organisation, general practice database) and high-risk populations (notifiable childhood infections database, children with a parental history of asthma or allergies, and infants with risk factors or a family association for atopy). The age of the participants ranged from birth to 14 years.

Outcomes assessed in the review
Studies that reported childhood asthma as diagnosed by a physician were eligible for inclusion. The studies had to assess, or provide data to assess, the association between asthma and antibiotic exposure. The main outcome was the risk of childhood asthma following at least one course of antibiotics versus none.

How were decisions on the relevance of primary studies made?
Two reviewers applied the inclusion criteria independently and any disagreements were resolved by consensus amongst all seven authors.
Assessment of study quality
Study quality was assessed using a modified published checklist. The published checklist has 27 items to assess reporting, internal and external validity and power, and a maximum score of 32 points. The modifications were not specified. An unspecified number of reviewers applied the checklist independently.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

The number of courses of antibiotics taken in the first year of life was extracted. Odds ratio (OR) or relative risk values for asthma were extracted with 95% confidence intervals (CIs), where reported, otherwise data to calculate unadjusted ORs were extracted (the number of participants and the number of asthma cases in the exposed and non-exposed groups in each study). If data to calculate the unadjusted OR for exposure to at least one antibiotic in the first year of life were not reported, they were requested from the study authors. Adjusted OR values reported in the included studies were extracted, together with data on the covariates used in the individual studies to adjust the ORs.

Methods of synthesis
How were the studies combined?
A meta-analysis was used to combine unadjusted ORs weighted by the inverse variance to obtain a pooled OR with 95% CI, calculated using a random-effects model.

A dose-response meta-analysis was conducted as follows. ORs adjusted for between one and seven covariates were reported in five of the included studies. For each study, these values were plotted against the number of courses of antibiotics taken during the first year of life. A log-linear regression line was fitted to obtain for each study an OR for the risk of asthma for each additional course of antibiotics taken. These ORs were then pooled in a random-effects meta-analysis.

Funnel plots were used to assess publication bias.

How were differences between studies investigated?
Prospective and retrospective studies were pooled separately as well as overall. Statistical heterogeneity in the meta-analysis was assessed using the chi-squared test (p<0.1 indicated statistical significance). Sources of heterogeneity were investigated using Galbraith and L'Abbe plots (not shown in the report). An 'influence analysis' was conducted to examine the influence of removing each individual study from the meta-analyses of prospective and retrospective studies. A subgroup meta-analysis was conducted in which studies in high-risk populations were separated from studies in the general population.

Results of the review
Nine studies were included: 4 prospective studies and 5 retrospective studies. The total number of participants was 33,211 (26,692 in the prospective studies and 6,519 in the retrospective studies).

The mean quality score was 17.4 for the prospective studies and 14.6 for the retrospective studies. No further details were reported.

A total of 12,082 participants and 1,817 asthma cases were included in the analysis of the risk of asthma following at least one course of antibiotics. A meta-analysis of 3 prospective studies (5,563 participants) showed no significant difference in the risk of asthma due to antibiotic exposure in the first year of life between exposed and non-exposed groups (unadjusted OR 1.12, 95% CI: 0.88, 1.42). The 5 retrospective studies (6,519 participants) showed an increased risk with antibiotic exposure that was statistically significant (OR 2.82, 95% CI: 2.07, 3.85, p=0.04), as did the pooled analysis of all 9 studies (OR 2.05, 95% CI: 1.41, 2.99, p<0.01). There was statistically significant heterogeneity between the retrospective studies. The subgroup comparison found no significant difference between the 3 studies in high-risk populations and those in the general population.
A total of 27,167 participants and 3,392 asthma cases were included in the dose-response analysis. Three prospective studies (25,755 participants) and 2 retrospective studies (1,412 participants) were included in the meta-analysis. Overall, there was no statistically significant difference in the OR for the risk of asthma for each additional course of antibiotics taken in the first year of life. Heterogeneity between the studies was statistically significant. The pooled OR from the 2 retrospective studies showed a significantly higher risk of asthma and no evidence of statistical heterogeneity.

The ‘influence analysis’ unsurprisingly showed that removal of individual studies from the meta-analyses could change the effect size and degree of heterogeneity.

There was no evidence of publication bias, although the analysis was limited by the small number of studies.

**Authors’ conclusions**
Exposure to antibiotics in the first year of life appeared to be a risk factor for the development of childhood asthma.

**CRD commentary**
The review addressed a clear question. The search covered a reasonable number of sources but the restriction to including only studies published in English raises concern about publication and language bias. There were too few included studies to enable a meaningful assessment of the potential for publication bias in the review. Methods were implemented to minimise errors and reviewer bias in the study selection and quality assessment, but possibly not in the data extraction process. Although the quality of the included studies was assessed systematically, the reporting of the findings was inadequate, mean composite scores gave no indication of the potential for bias or confounding in the individual studies, and insufficient information was given to make an independent judgment.

Individual study characteristics were not reported in sufficient detail to judge if the studies were sufficiently similar to combine. Notably, antibiotic exposure in the included studies was not reported. The meta-analysis was conducted using standard methods but with insufficient caution with regard to pooling data from observational studies, hence the results could be misleading. The authors emphasised in their discussion that the included studies had numerous methodological limitations. Those limitations cast serious doubt on the reliability of the results. The strength of the evidence was not sufficient to support a firm conclusion.

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

Research: The authors stated that large prospective administrative database studies are needed to determine the risk of asthma following antibiotic use in children stratified by site of infection, type of antibiotics and other confounding factors. Studies are needed in population-based samples and in high-risk populations. Studies should use validated measures of exposure and outcome, and follow-up should be at least 1 year after antibiotic exposure.

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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.