Systematic review of the treatment of upper respiratory tract infection

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Authors' objectives
To assess the risks and benefits of antibiotic treatment in children with symptoms of upper respiratory tract infection.

Searching
MEDLINE (from 1966) and EMBASE (from 1982) were searched to 1994 using the Cochrane Collaboration search strategy with the following MESH terms: cough; bronchitis; sputum; and respiratory tract infection. The search was not restricted to English language studies. The Science Citation Index was searched and references in published studies and abstracts were searched especially for studies before 1966. The Controlled Trials Register from the Cochrane Library was searched using the terms bronchitis, chest infection and common cold. Authors of published RCTs and UK drug companies listed as involved in the manufacture of antibiotics according to the British National Formulary were contacted for information on unpublished trials.

Study selection
Study designs of evaluations included in the review
Prospective randomised placebo controlled trials (RCTs) that compared antibiotic treatment with placebo in children with URTI managed in community settings were included if the antibiotic was allocated by formal randomisation or by quasi randomisation. Comparative studies between different classes of antibiotics were excluded. Two trials that assessed management of URTI in children with persistent cough (> 10 days) were excluded from the principal results of the meta-analysis. A further 4 RCTs were excluded from the meta-analysis because outcomes were reported as a rate with no actual data on the number of children assessed at the end of the trial.

Maximal follow-up period of trials included in the meta-analysis was 14 days.

Specific interventions included in the review
The following antibiotics were compared to placebo: gantrisin, penicillin, aureomycin, sulphonamides, tetracyclines, chloramphenicol, ampicillin, erythromycin, co-trimoxazole, cephalexin, and amoxycillin/clavullinic acid. Duration of therapy ranged from 2 to 10 days.

Participants included in the review
Subjects studied were children aged 0 to 12 years who were attending a family practice clinic, hospital based out-patient department or community based health clinic with onset of acute upper respiratory illness (URTI) in the previous two weeks. URTI was defined, according to the International Classification of Health Problems in Primary Care, as the acute inflammation of nasal or pharyngeal mucosa in the absence of other specifically defined respiratory infection. Only children with non-specific symptoms referable to the respiratory tract which had not been treated in the previous week with antibiotics were included.

Outcomes assessed in the review
The following outcomes were assessed: the proportion of children in whom clinical outcome was worse or unchanged at day 5 to 7; the proportion of children who suffered complications or progression of illness (defined in individual trials as either otitis media or progression of respiratory symptoms including pharyngitis, bronchitis or pneumonia); and the proportion of children who had side-effects (including diarrhoea and vomiting, rashes, hyperactivity and stomatitis).

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the authors performed the selection.

Assessment of study quality
The quality of each study was assessed according to the following criteria in the Cochrane Collaboration Handbook: selection bias; performance bias; attrition bias; and detection bias. Each study was assessed independently by two researchers with each validity criterion being scored from 1 to 3 giving a highest score of 12. Measurement of agreement was calculated using the Kappa statistic with disagreements being resolved by consensus.

Data extraction
Data were extracted independently and where data were missing or incomplete the authors of the trial were contacted for clarification. Extracted data included the following: author; year published; number of participants; age of children; setting; diagnostic label; clinical features; antibiotic dosage; antibiotic duration; and outcomes measured.

Methods of synthesis
How were the studies combined?
Pooled relative risks (RR) with 95% confidence limits were calculated using a fixed-effect model provided by REVMAN 3.0.

How were differences between studies investigated?
The magnitude of baseline risk and heterogeneity was explored using a L’Abbe plot (see Other Publications of Related Interest).

Results of the review
Ten RCTs are included in the review (N = 3626 children). Of these 6 RCTs contributed to the meta-analysis (N = 3501 children).

Five RCTs were used to assess clinical condition worse or unchanged at follow-up (N = 1482 children).

Five RCTs were used to determine complications or progression of illness (N = 842 children).

Five RCTs were used to determine the incidence of side-effects (N = 1448 children).

The quality of RCTs was variable with validity scores ranging from 4 to 10. Kappa for between-investigator agreement of RCT quality was 0.79.

Baseline risk: The proportion of children in whom clinical outcome was worse or unchanged ranged from 5% to 69% in the placebo arm. Risk for progression of illness ranges from 2% to 15%.

Clinical condition worse or unchanged at follow-up with antibiotic vs placebo: RR = 1.01 (95%CI: 0.90, 1.13).

Complications or progression of illness with antibiotic vs placebo: RR = 0.71 (95%CI: 0.45, 1.12).

Side-effects with antibiotic vs placebo: RR = 0.8 (95%CI: 0.54, 1.21).

Authors' conclusions
In view of the lack of efficacy and low complication rates of upper respiratory tract infection, antibiotic treatment of children with upper respiratory tract infection is not supported by current evidence from randomised trials.

CRD commentary
This clearly written and presented review included a stated aim, comprehensive literature search, defined inclusion and validity criteria with reasons for exclusion of some trials from the meta-analysis, details of methods used to extract data and assess validity, assessment of heterogeneity and relevant details of primary studies. The authors discuss the following limitations of the review: contributing trials were small with inadequate power and the review cannot rule out a small but clinically important treatment effect with antibiotics; the efficacy of antibiotics may be greater in a sub-
group of children who have a higher baseline risk of developing complications; the imprecision of the clinical diagnosis of URTI in terms of the likely resolution of illness; published reports from 4 of the 10 trials did not contain any useable data and it was not possible to contact the authors; two trials reported a beneficial effect from antibiotic treatment but were not included.

The evidence supports the author's conclusions.

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

Practice: The management of upper respiratory tract infection should be based on a full explanation of the likely course of the illness to the child's parents and symptomatic treatment in the first instance.

Research: The authors state that a larger fully powered study is required to determine the size and precision of any effects of antibiotics on complications of upper respiratory tract infection or progression of disease. Further studies are required to delineate the symptoms and signs of URTI and their prognostic significance. Assessment of efficacy of antibiotics in children with persistent cough requires further investigation before antibiotic treatment can be recommended.

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