Systematic review of the treatment of upper respiratory tract infection

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Abstract

Objectives—To assess the risks and benefits of antibiotic treatment in children with symptoms of upper respiratory tract infection (URTI).

Design—Quantitative systematic review of randomised trials that compare antibiotic treatment with placebo.

Data sources—Twelve trials retrieved from a systematic search (electronic databases, contact with authors, contact with drug manufacturers, reference lists); no restriction on language.

Main outcome measures—The proportion of children in whom the clinical outcome was worse or unchanged; the proportion of children who suffered complications or progression of illness; the proportion of children who had side effects.

Results—1699 children were randomised in six trials that contributed to the meta-analysis. Six trials were not used in the meta-analysis because of different outcomes or incomplete data. Clinical outcome was not improved by antibiotic treatment (relative risk 1.01, 95% confidence interval (CI) 0.90 to 1.13), neither was the proportion of children suffering from complications or progression of illness (relative risk 0.71, 95% CI 0.45 to 1.12). Complications from URTI in the five trials that reported this outcome was low (range 2–15%). Antibiotic treatment was not associated with an increase in side effects compared with placebo (relative risk 0.8, 95% CI 0.54 to 1.21).

Conclusions—In view of the lack of efficacy and low complication rates, antibiotic treatment of children with URTI is not supported by current evidence from randomised trials.

Keywords: respiratory tract infections; systematic review; meta-analysis; antibiotics

Upper respiratory tract infection (URTI) in children is a common illness and accounts for a substantial proportion of consultations to family doctors in the UK. The fourth National Morbidity Survey reports consultation rates of 3103 and 1002 per 10 000 years at risk in children aged 0–4 and 5–15 years, respectively. The clinical syndrome of URTI comprises a variety of symptoms—most frequently cough and coryza associated with fever. The cause is usually viral, with fewer than 10% of cases caused by bacteria. URTI forms a continuum with lower respiratory tract infection, which is more often associated with bacterial infection. Haemophilus influenzae and Streptococcus pneumoniae are cultured in approximately 20% of children with lower respiratory tract infection in the community.

Despite the predominantly viral cause, antibiotics are frequently prescribed to children with symptoms of URTI. On average, 40% of children with URTI are prescribed an antibiotic, but this varies substantially between doctors, with some general practitioners prescribing to as many as 60% of children who present with URTI. Such prescribing is initiated by general practitioners in the belief that antibiotics may either ameliorate symptoms, shorten the illness, or prevent further complications, such as pneumonia or acute otitis media. This belief is not based on any firm evidence from clinical trials. In fact, previous narrative reviews have suggested that for most children URTI is a self limiting condition that requires symptomatic treatment alone, and that antibiotic treatment is more likely to cause harm than benefit.

In view of the persistence of antibiotic prescribing for this condition and the uncertainty concerning the risks and benefits from treatment, we performed a quantitative systematic review of randomised controlled trials (RCTs) that compared antibiotic treatment with placebo in children with URTI managed in community settings.

Methods

INCLUSION AND EXCLUSION CRITERIA

We included studies of infants and children aged 0–12 years who were attending a family practice clinic, hospital based outpatient department, or community based health clinic, with onset of acute upper respiratory illness in the previous two weeks. The definition of URTI was pragmatic one. We included studies of children with non-specific symptoms referable to the respiratory tract, which had not been treated in the preceding week with antibiotics. Therefore, we accorded with the definition of the International Classification of Health Problems in Primary Care (ICHPPC-2), which defines URTI as the acute inflammation of nasal or pharyngeal mucosa in the absence of other specifically defined respiratory infection. The studies included were prospective RCTs where antibiotic was allocated by formal randomisation or by quasi-randomisation such as alternation, to treatment and placebo groups. Only placebo controlled trials were included, comparative studies between different classes of antibiotics were excluded. The outcomes in this review...
Table 1 Characteristics of population, diagnostic labels, and clinical features

<table>
<thead>
<tr>
<th>Trial</th>
<th>Year published</th>
<th>Number of participants</th>
<th>Age of children</th>
<th>Setting</th>
<th>Diagnostic label</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hardy (1993)</td>
<td>1956</td>
<td>217</td>
<td>0 to 13 years</td>
<td>Outpatient clinic</td>
<td>Uncomplicated respiratory infections</td>
<td>Fever ≥ 38°C Negative clinical examination except for nasopharyngitis</td>
</tr>
<tr>
<td>Townsend (1960)</td>
<td>1971</td>
<td>849</td>
<td>2 months to 12 years</td>
<td>Private US paediatric practice</td>
<td>Suspected viral respiratory infection</td>
<td>Not reported</td>
</tr>
<tr>
<td>Wynn-Williams (1961)</td>
<td>1977</td>
<td>197</td>
<td>2 to 12 years</td>
<td>Community setting in UK</td>
<td>Families selected and then randomised from children with &quot;past history of frequent colds going onto the chest&quot;. Initiation of treatment if mother suspected URI in child &quot;severe enough to put child to bed or prevent attendance at school&quot;</td>
<td>Not reported</td>
</tr>
<tr>
<td>Ackerman (1968)</td>
<td>1962</td>
<td>781</td>
<td>0 to 12 years</td>
<td>Private US paediatric practice</td>
<td>Children with a &quot;febrile respiratory illness&quot;</td>
<td>All &quot;presented signs and symptoms of the respiratory system&quot;. Cases further classified into measles, croup, and others</td>
</tr>
<tr>
<td>Townsend (1960)</td>
<td>1968</td>
<td>60</td>
<td>3 to 12 months</td>
<td>US army dispensary</td>
<td>Undifferentiated respiratory infection</td>
<td>Rectal temperature &gt; 38°C Fever ≥ 39°C</td>
</tr>
<tr>
<td>Lexomboon (1971)</td>
<td>1977</td>
<td>174</td>
<td>6 months to 12 years (half &lt; 2 years)</td>
<td>Outpatient department hospital in Thailand</td>
<td>Upper respiratory infection</td>
<td>Symptoms of RTI &lt; 48 h Symptoms referable to respiratory tract, most had cough and running nose, no antibiotic in previous week</td>
</tr>
<tr>
<td>Gordon (1974)</td>
<td>1969</td>
<td>89</td>
<td>&lt; 2 years to 6 years</td>
<td>A &amp; E department in children's hospital, Australia</td>
<td>Minor respiratory illness</td>
<td>Classified as having nasopharyngitis (42), pharyngo-tonsillitis (71), bronchitis or laryngotracheo-bronchitis (84)</td>
</tr>
<tr>
<td>Taylor (1977)</td>
<td>1972</td>
<td>197</td>
<td>2 to 10 years</td>
<td>Suburban general practice in New Zealand</td>
<td>Presumed viral respiratory infections</td>
<td>All had purulent nasal discharge with or without other signs of respiratory illness</td>
</tr>
<tr>
<td>Todd (1984)</td>
<td>1984</td>
<td>142</td>
<td>&gt; 2 months; mean (SD) 2 (2 years)</td>
<td>2 paediatric offices and 1 clinic in army base in US</td>
<td>Purulent nasopharyngitis</td>
<td>Mild acute respiratory infection defined according to WHO criteria: mild upper respiratory signs such as cough, runny nose and/or fever &gt;37°C Respiratory rate &lt; 50/min</td>
</tr>
<tr>
<td>Sutrisna (1991)</td>
<td>1991</td>
<td>900</td>
<td>&lt; 5 years; 38% (antibiotic) 35% (placebo) were infants</td>
<td>Health clinics in Indonesia</td>
<td>Mild acute respiratory infection</td>
<td>Persistent cough &gt; 10 days seeking medical help. Excluded clinically suspected pertussis (known exposure or whooping) Persistent cough was defined as cough for a minimum of 10 days. Children with frequent cough, ≥ 11 coughing attacks/24 h were included</td>
</tr>
<tr>
<td>Darelid (1993)</td>
<td>1993</td>
<td>88</td>
<td>6 months to 6 years</td>
<td>3 paediatric outpatient departments in Sweden</td>
<td>Longstanding Moraxella catarrhalis associated cough</td>
<td>Lower respiratory infection with cough for a minimum of 10 days. Children with frequent cough, ≥ 11 coughing attacks/24 h were included</td>
</tr>
<tr>
<td>Gottfarb (1994)</td>
<td>1994</td>
<td>37</td>
<td>7 months to 7 years</td>
<td>3 paediatric outpatient departments in Sweden</td>
<td>Persistent cough</td>
<td>Persistent cough &gt; 10 days seeking medical help. Excluded clinically suspected pertussis (known exposure or whooping) Persistent cough was defined as cough for a minimum of 10 days. Children with frequent cough, ≥ 11 coughing attacks/24 h were included</td>
</tr>
</tbody>
</table>

*Not included in the principal results of the meta-analysis.

We searched MEDLINE and EMBASE databases from 1966 and 1982, respectively, using the recommended Cochrane Collaboration search strategy, using the following Medical Subject Headings (MESH) terms: cough, bronchitis, sputum, respiratory tract infection. The search was not restricted to the English language. We also searched for references from published research by using Science Citation Index and searching references in published studies and abstracts, particularly for those published before 1966. We conducted a search on the controlled trials register from the Cochrane Library, using the search terms bronchitis, chest infection or common cold. We contacted authors of published RCTs requesting knowledge of any unpublished studies. We also wrote to all UK drug companies who manufacture antibiotics according to the British National Formulary requesting unpublished RCTs.

**SYSTEMATIC SEARCH**

We searched MEDLINE and EMBASE databases from 1966 and 1982, respectively, using the recommended Cochrane Collaboration search strategy, using the following Medical Subject Headings (MESH) terms: cough, bronchitis, sputum, respiratory tract infection. The search was not restricted to the English language. We also searched for references from published research by using Science Citation Index and searching references in published studies and abstracts, particularly for those published before 1966. We conducted a search on the controlled trials register from the Cochrane Library, using the search terms bronchitis, chest infection or common cold. We contacted authors of published RCTs requesting knowledge of any unpublished studies. We also wrote to all UK drug companies who manufacture antibiotics according to the British National Formulary requesting unpublished RCTs.
means of the κ statistic and disagreement resolved by consensus. Data were extracted independently and where data were missing or incomplete the authors of the trial were contacted and clarification was sought.

TABLE 2 Interventions, outcomes, and quality of trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Antibiotic dosage</th>
<th>Antibiotic duration</th>
<th>Outcomes measured</th>
<th>Contribution to meta-analysis</th>
<th>Quality</th>
<th>Favour antibiotic?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hardy¹¹</td>
<td>Gantrisin, penicillin or aureomycin, dosage not stated but antibiotic given &quot;adjusting the dosage according to a predetermined scale, based on weight and age&quot;. Given qid Sulphonamides 0.1 g/kg/24 h Tetracyclines 40–50 mg/kg/24 h Another group of children randomised to &quot;prophylactic&quot; treatment, of same drugs at &quot;approximately ¼ of the therapeutic dose&quot;.</td>
<td>4 days</td>
<td>Complication rate in a two week period</td>
<td>Yes, outcome 2</td>
<td>7</td>
<td>No</td>
</tr>
<tr>
<td>Townsend¹²</td>
<td>Sulphonamides (0.5 g per teaspoonful) Tetracycline (125 mg per teaspoonful) Chloramphenicol (125 mg per teaspoonful) Penicillin (20000 units per teaspoonful) All given by a dosage schedule Penicillin V (100000 units qid) Tetracycline 50 mg qid</td>
<td>Not stated</td>
<td>Complication rate</td>
<td>No</td>
<td>4</td>
<td>No</td>
</tr>
<tr>
<td>Wynn-Williams¹³</td>
<td>Tetracycline given tid in the following dose: age 2: 40 mg; age 3 and 4: 50 mg; age 5 and 6: 75 mg; age 7 and 8: 100 mg; ages 9 to 12: 150 mg</td>
<td>2 days</td>
<td>Subsequent URIs (measured as episodes)</td>
<td>Average duration of symptoms</td>
<td>7</td>
<td>Yes</td>
</tr>
<tr>
<td>Townsend¹³</td>
<td>Sulphonamides (0.1 g/kg/24 h) Tetracycline (125 mg per kg/24 h) Chloramphenicol (125 mg per kg/24 h) Penicillin (20000 units per kg/24 h) All given by a dosage schedule Penicillin V (100000 units qid)</td>
<td>For as long as child was febrile</td>
<td>No</td>
<td>6</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Ackerman¹⁶</td>
<td>Penicillin 30 mg/kg/day Tetracycline 40 mg/kg/day Ampicillin Erythromycin Dosage 125 mg/5 ml Age &lt; 2 years: 3 to 5 ml qid Older children: 5 to 10 ml qid Amoxycillin (125 ml/5 ml) Co-trimoxazole (sulphamethoxazole 200 mg and trimethoprim 40 mg/5 ml)</td>
<td>7 days</td>
<td>Clinical state at follow up (48 h)</td>
<td>Yes, outcome 1, 2, and 3</td>
<td>10</td>
<td>No</td>
</tr>
<tr>
<td>Gordon¹⁶</td>
<td>Penicillin Ampicillin Erythromycin Dosage 125 mg/5 ml Age &lt; 2 years: 3 to 5 ml qid Older children: 5 to 10 ml qid Amoxycillin (125 ml/5 ml) Co-trimoxazole (sulphamethoxazole 200 mg and trimethoprim 40 mg/5 ml)</td>
<td>Not stated</td>
<td>Relief of symptoms</td>
<td>Yes, outcome 1</td>
<td>7</td>
<td>No</td>
</tr>
<tr>
<td>Taylor¹⁶</td>
<td>Penicillin 30 mg/kg/day Tetracycline 40 mg/kg/day Ampicillin Erythromycin Dosage 125 mg/5 ml Age &lt; 2 years: 3 to 5 ml qid Older children: 5 to 10 ml qid Amoxycillin (125 ml/5 ml) Co-trimoxazole (sulphamethoxazole 200 mg and trimethoprim 40 mg/5 ml)</td>
<td>5 days</td>
<td>Treatment failure</td>
<td>Yes, outcomes 1, 2, and 3</td>
<td>8</td>
<td>Yes (treatment failure) No (other outcomes)</td>
</tr>
<tr>
<td>Todd¹¹</td>
<td>Cephalexin 25–50 mg/kg/day</td>
<td>5 to 6 days</td>
<td>Assessed at day 5 to 6 Parent assessed: drug benefit drug side effects Physician assessed: fever nasal discharge complications</td>
<td>Yes, outcomes 1, 2, and 3</td>
<td>9</td>
<td>No</td>
</tr>
<tr>
<td>Sutrisna²²</td>
<td>Amoxicillin (25–30 mg/kg) qid</td>
<td>5 days</td>
<td>Clinical outcome at 5–7 and 14 days</td>
<td>Yes, outcomes 1 and 3</td>
<td>7</td>
<td>No</td>
</tr>
<tr>
<td>Darell¹¹*</td>
<td>Erythromycin suspension 50 mg/kg/day</td>
<td>7 days</td>
<td>Cough at 7 days</td>
<td>No</td>
<td>8</td>
<td>Yes, but open trial, parent and investigator knew treatment assignment</td>
</tr>
<tr>
<td>Gottfarb¹¹*</td>
<td>Amoxicillin/clavulanic acid 20 mg/kg/day</td>
<td>7 days</td>
<td>Number of coughing attacks each day for 8 days Clinical improvement judged by parents day 12 Clinical improvement judged by doctor day 12</td>
<td>No</td>
<td>6</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Outcomes coded as follows:
1, the proportion of children in whom the clinical outcome is unchanged or worse.
2, the proportion of children who suffered complications or progression of illness.
3, the proportion of children who had suffered side effects from taking antibiotic or placebo.
*Not included in the principal results of the meta-analysis.

ANALYSIS
Statistical and clinical significance was evaluated by means of estimating relative risk.¹¹ The magnitude of baseline risk and heterogeneity between studies was explored by means of a L’Abbe graph.¹² Pooled relative risks were estimated with 95% confidence intervals (CI) by means of a fixed effects model.¹³ Relative risks and pooling of data were calculated with REV-MAN 3.0 (Update Software 1996, Oxford, UK).

RESULTS
TRIALS FOUND AND QUALITY RATING
We found 12 randomised trials that matched the inclusion criteria of the study (tables 1 and
This review demonstrates that antibiotic treatment of children with URTI does not alter the clinical outcome of the illness or prevent and in view of the different characteristics of the children at the time of recruitment these were not included in the principal results of the meta-analysis. Both of these trials reported that antibiotic treatment has a beneficial effect on clinical outcome (table 2).

Of the 10 remaining RCTs, six contributed data to the meta-analysis. The other four RCTs did not contribute data because the outcome was reported as a rate, with no actual data on the number of children assessed at the end of the trial. Three of these four trials reported that antibiotic treatment had no effect on either relief of symptoms or subsequent complications in children (table 2).

The quality of RCTs was variable, with a range of 4 to 10 in terms of overall quality score. The k score for the between-investigator assessment of RCT quality was 0.79 indicating a substantial agreement in quality rating of the separate RCTs.

**BASELINE RISK AND DIAGNOSIS**

There was a substantial difference between individual RCTs in the proportion of children in whom the clinical outcome was worse or unchanged (range in placebo arms of individual trials 5–69%) (fig 1). This finding highlights the heterogeneous nature of the participants in each of the studies in terms of the natural resolution from URTI. In contrast, the baseline risk for progression of illness or further complications was less variable (range 2–15%) (fig 1).

**EFFICACY AND SIDE EFFECTS OF ANTIBIOTIC**

Clinical condition worse or unchanged at follow up (relative risk 1.13, 95% CI 0.97 to 1.31) and complications or progression of illness (relative risk 0.71, 95% CI 0.5 to 1.2) were different for antibiotic treatment and placebo groups (figs 2 and 3). The complications from illness were not reported at a uniform time interval in all studies, the maximum time of reporting after initial treatment was two weeks. Side effects from treatment were not significantly associated with antibiotic use (relative risk 0.8, 95% CI 0.5 to 1.2) (fig 4).

**Discussion**

This review demonstrates that antibiotic treatment of children with URTI does not alter the clinical outcome of the illness or prevent

**Key messages**

- Antibiotic treatment did not alter clinical outcome or reduce complication rates in children with upper respiratory tract infections
- Side effects were similar in antibiotic treatment and placebo groups
- Complications from upper respiratory tract infections are low (2–15%)
- Larger trials are needed to establish whether antibiotic treatment reduces complications in children with upper respiratory tract infections
Systematic review of the treatment of URTI

<table>
<thead>
<tr>
<th>Study</th>
<th>Expt n/N</th>
<th>Ctrl n/N</th>
<th>Relative risk (95% CI fixed)</th>
<th>Weight %</th>
<th>RR (95% CI fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ackerman</td>
<td>11/40</td>
<td>8/20</td>
<td>25.2 0.69 [0.33, 1.43]</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Hardy</td>
<td>4/149</td>
<td>0/88</td>
<td>1.6 4.16 [0.23, 75.83]</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Sutrisna</td>
<td>4/451</td>
<td>7/449</td>
<td>16.6 0.57 [0.17, 1.93]</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Taylor</td>
<td>26/129</td>
<td>11/59</td>
<td>35.7 1.08 [0.57, 2.04]</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Todd</td>
<td>4/46</td>
<td>8/37</td>
<td>20.9 0.40 [0.13, 1.23]</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Total (95% Cl)</td>
<td>49/815</td>
<td>34/633</td>
<td>100.0 0.80 [0.54, 1.21]</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Chi-square 4.01 (df = 4) Z = 1.05

Figure 4 Side effects of treatment in children with upper respiratory tract infection treated with antibiotic vs placebo.

We thank Matthias Egger, David Jewell, and Debbie Sharp for helpful comments on this paper, and Johan Darelid for clarifica-

... further complications (figs 2 and 3). Furthermore, the reported complication rate in the placebo arms of the RCTs included confirms that most cases of URTI resolve without further problems, with complications ranging from 2% to 15% in the four trials that examined this outcome (fig 1). Antibiotic treatment was not associated with a significant risk of side effects but the range of reported side effects in the antibiotic arms of included RCTs was wide (1% to 28%).

These results are consistent with previous reviews of URTI in children that questioned the role of antibiotic treatment. Observational research in a cohort of 965 children in UK general practice reported no correlation between antibiotic treatment and subsequent complication rate. The complication rate of 6% in observational research is consistent with the range of complications reported in the individual RCTs in this systematic review (fig 1).

There are shortcomings to this systematic review that need to be addressed. First, with the exception of Sutrisna et al, all trials that contributed to the meta-analysis were small with inadequate power to detect clinically important differences between antibiotic treatment and placebo. Pooling a small number of trials each of which has not recruited many subjects makes a systematic review of such trials prone to error and potential bias. This systematic review cannot rule out a small but possibly clinically important treatment effect with antibiotics. A larger fully powered study is required to determine the size and precision of any effects of antibiotics on complications of URTI or progression of disease. Of the complications that occurred, 30% were diagnosed as otitis media, 17% as pneumonia, and the rest classified as a variety of upper respiratory complications. The efficacy of antibiotic treatment may indeed be greater in a subgroup of children who have a higher baseline risk of developing complications. Further study is needed to test the hypothesis that children at higher risk of complications benefit from antibiotic treatment. Second, the range of clinical outcome at follow up in the individual RCTs (fig 1) shows that the clinical diagnosis of URTI is imprecise in terms of the likely resolution of illness. Further studies are needed to delineate the symptoms and signs of URTI and their prognostic significance. Third, four of 10 trials did not provide any data, principally because authors could not be contacted as the trial had been published some years ago and the published report did not contain usable data. Only one of these trials reported a positive effect of antibiotic treatment. Lastly, two trials reported a beneficial effect of antibiotic treatment but were not included in the pooled analysis in this review. In view of the small number of patients recruited to these two RCTs and the fact that one trial was an unblinded study, assessment of efficacy in children with persistent cough requires further evaluation before antibiotic treatment can be recommended for these children.

Why do general practitioners continue to prescribe antibiotics for URTI? First, they may be too cautious when managing URTI, overestimating the likely complications, with a lowered threshold for antibiotic prescribing. Second, general practitioners may feel that parents of children with URTI expect a prescription for an antibiotic. Evidence from adults presenting with URTI refutes this assumption. Patients with URTI are more satisfied when doctors explain the nature of likely course of their illness. Thus, like the management of acute otitis media, the management of URTI should be reassessed in terms of the natural course of the illness and the low rate of complications.

There are other serious consequences that need to be considered in the context of a policy of prescribing antibiotics for URTI. Observational research has shown that 24% of children are re-evaluated by a general practitioner during the same episode of URTI. Antibiotic use in adults with sore throat “medicalises” a self limiting condition and increases patient expectation for reattendance and antibiotic treatment when a recurrent episode of illness occurs. It seems likely that continuing to prescribe antibiotics for URTI is likely to increase parental expectations, influencing both prescribing and reattendance rates. Lastly, antibiotic use in the UK is increasing and is associated with the emergence of resistant organisms. These considerations emphasise that antibiotic treatment is not a risk free policy; careful measurement of the likely benefit and harm of treatment is required for all cases of URTI.

In conclusion, URTI in children is usually a self limiting condition with complications occurring in approximately 10% of cases. Antibiotic treatment does not influence either the course of illness or the likelihood of suffering complications. In view of the adverse effects on reattendance, “medicalisation” of a self limiting condition, costs of treatment, and impact on antibiotic resistant organisms, the management of URTI 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.

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tion concerning data from his study. This study was funded by The Royal College of General Practitioners Scientific Foundation Board.


