Systematic review of the treatment of upper respiratory tract infection

Tom Fahey, Nigel Stocks, Toby Thomas

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.

(Arch Dis Child 1998;79:225–230)

Keywords: respiratory tract infections; systematic review; meta-analysis; antibiotics
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††</td>
<td>1956</td>
<td>217 randomised, 118 male, 99 female; 149 analysed (68.7% follow up)</td>
<td>0 to 13 years</td>
<td>Outpatient clinic</td>
<td>Uncomplicated respiratory infections</td>
<td>Fever $\geq$ 38°C</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Negative clinical examination</td>
<td>except for nasopharyngitis</td>
</tr>
<tr>
<td>Townsend‡‡</td>
<td>1962</td>
<td>781 children</td>
<td>0 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‡‡</td>
<td>1961</td>
<td>96 children</td>
<td>2 to 12 years</td>
<td>Community setting in UK</td>
<td>Families selected and then randomised from children</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‡‡</td>
<td>1962</td>
<td>845 children (total number of cases seen in 1884)</td>
<td>2 months to 12 years</td>
<td>Private US paediatric practice</td>
<td>Children with a &quot;febrile respiratory illness&quot;</td>
<td></td>
</tr>
<tr>
<td>Ackerman‡‡</td>
<td>1968</td>
<td>60 children</td>
<td>3 to 12 months</td>
<td>US army dispensary</td>
<td>Undifferentiated respiratory infection</td>
<td></td>
</tr>
<tr>
<td>Lexomboon‡‡</td>
<td>1971</td>
<td>174 children</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>Rectal temperature $\geq$ 38°C</td>
</tr>
<tr>
<td>Gordon‡‡</td>
<td>1974</td>
<td>89 children</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>Symptoms of RTI $&lt; 48$ h</td>
</tr>
<tr>
<td>Taylor</td>
<td>1977</td>
<td>197 children</td>
<td>2 to 10 years</td>
<td>Suburban general practice in New Zealand</td>
<td>Presumed viral respiratory infections</td>
<td>Classified as having nasopharyngitis (42), bronchitis or laryngotracheo-bronchitis (84)</td>
</tr>
<tr>
<td>Todd‡†</td>
<td>1984</td>
<td>142 children</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>All had purulent nasal discharge with or without other signs of respiratory illness</td>
</tr>
<tr>
<td>Sutrisna‡‡</td>
<td>1991</td>
<td>900 children</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>Mild acute respiratory infection defined according to WHO criteria: mild upper respiratory signs such as cough, runny nose and/or fever ($&gt;37^\circ$C) Respiratory rate $&lt; 50$/min</td>
</tr>
<tr>
<td>Darelid‡‡**</td>
<td>1993</td>
<td>88 children</td>
<td>6 months to 6 years</td>
<td>3 paediatric outpatient departments in Sweden</td>
<td>Longstanding Moraxella catarrhalis associated cough</td>
<td>Persistent cough $&gt; 10$ days seeking medical help. Excluded clinically suspected pertussis (known exposure or whooping)</td>
</tr>
<tr>
<td>Gottfarb‡‡**</td>
<td>1994</td>
<td>37 children</td>
<td>7 months to 7 years</td>
<td>3 paediatric outpatient departments in Sweden</td>
<td>Persistent cough</td>
<td>Lower respiratory infection with cough for a minimum of 10 days. Children with frequent cough, $\geq 11$ coughing attacks/24 h were included</td>
</tr>
</tbody>
</table>

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

were: the proportion of children in whom clinical outcome was worse or unchanged at day 5–7; 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).

**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.

**QUALITY ASSESSMENT AND EXTRACTION OF DATA**

Each trial was read independently by two authors who then assessed the quality of each study according to the four criteria outlined in the Cochrane collaboration handbook. Each criterion—selection bias, performance bias, attrition bias, and detection bias—was scored from 1 to 3, so the highest score for an individual trial was 12. Measurement of agreement between reviewers was calculated by...
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.

**ANALYSIS**

Statistical and clinical significance was evaluated by means of estimating relative risk. The magnitude of baseline risk and heterogeneity between studies was explored by means of a

**RESULTS**

**TRIALS FOUND AND QUALITY RATING**

We found 12 randomised trials that matched the inclusion criteria of the study (tables 1 and 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>Favours antibiotic?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hardy</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>Townsend</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 Sulphonamides (0.5 g per teaspooonful) Tetracycline (125 mg per teaspooonful) Chloramphenicol (125 mg per teaspooonful) Penicillin (200000 units per teaspooonful) All given by a dosage schedule</td>
<td>Not stated</td>
<td>Complication rate</td>
<td>No</td>
<td>4</td>
<td>No</td>
</tr>
<tr>
<td>Wynn-Williams</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 Sulphonamides (0.5 g per teaspooonful) Tetracycline (125 mg per teaspooonful) Chloramphenicol (125 mg per teaspooonful) Penicillin (200000 units per teaspooonful) All given by a dosage schedule</td>
<td>2 days</td>
<td>Subsequent URIs (measured as episodes)</td>
<td>No</td>
<td>7</td>
<td>Yes</td>
</tr>
<tr>
<td>Townsend</td>
<td>Tetracycline (125 mg per teaspooonful) Chloramphenicol (125 mg per teaspooonful) Penicillin (200000 units per teaspooonful) All given by a dosage schedule</td>
<td>For as long as child was febrile</td>
<td>Not given</td>
<td>No</td>
<td>6</td>
<td>No</td>
</tr>
<tr>
<td>Ackerman</td>
<td>Penicillin V (100000 units qid) Tetracycline 50 mg qid</td>
<td>10 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>Lexomboon</td>
<td>Penicillin 30 mg/kg/day Tetracycline 40 mg/kg/day</td>
<td>7 days</td>
<td>Treatment failure</td>
<td>No</td>
<td>5</td>
<td>No</td>
</tr>
<tr>
<td>Gordon</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</td>
<td>Not stated</td>
<td>Reliefe of symptoms</td>
<td>No</td>
<td>5</td>
<td>No</td>
</tr>
<tr>
<td>Taylor</td>
<td>Amoxicillin (125 ml/5 ml) Co-trimoxazole (sulphamethoxazole 200 mg and trimethoprim 40 mg/5 ml)</td>
<td>5 days</td>
<td>Treatment failure Symptoms at day 8</td>
<td>Yes, outcomes 1, 2, and 3</td>
<td>8</td>
<td>Yes (treatment failure) No (other outcomes)</td>
</tr>
<tr>
<td>Todd</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>Sutrisna</td>
<td>Ampicillin (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>Darelid</td>
<td>Erythromycin suspension 50 mg/kg/day</td>
<td>7 days</td>
<td>Cough at 7 days Worsening cough, fever and purulent sputum Side effects</td>
<td>No</td>
<td>8</td>
<td>Yes, but open trial, parent and investigator knew treatment assignment</td>
</tr>
<tr>
<td>Gottfarb</td>
<td>A moxycillin/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.

Pooled relative risks were estimated with 95% confidence intervals (CI) by means of a fixed effects model. Relative risks and pooling of data were calculated with REV- MAN 3.0 (Update Software 1996, Oxford, UK).
Figure 1  L'Abbé plots of the proportion of children in whom (A) the clinical outcome was worse or unchanged and (B) who suffered complications or progression of illness.

2). A further unpublished RCT from the 1950s was mentioned in a report from a conference proceeding,14 but we were unable to secure any data from this study (unable to contact authors). Of the 12 studies, two were concerned with management of URTI in children with persistent cough (>10 days),15 16 to secure any data from this study (unable to contact authors). Of the 12 studies, two were concerned with management of URTI in children with persistent cough (>10 days),15 16

<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>7/40</td>
<td>5/20</td>
<td>2.3</td>
<td>0.70</td>
<td>0.25–1.93</td>
</tr>
<tr>
<td>Lexomboon</td>
<td>8/174</td>
<td>4/87</td>
<td>1.8</td>
<td>1.00</td>
<td>0.31–3.23</td>
</tr>
<tr>
<td>Sutrisna</td>
<td>243/447</td>
<td>233/442</td>
<td>80.7</td>
<td>1.03</td>
<td>0.91–1.17</td>
</tr>
<tr>
<td>Taylor</td>
<td>22/129</td>
<td>11/59</td>
<td>5.2</td>
<td>0.91</td>
<td>0.48–1.76</td>
</tr>
<tr>
<td>Todd</td>
<td>29/45</td>
<td>27/39</td>
<td>10.0</td>
<td>0.93</td>
<td>0.69–1.26</td>
</tr>
<tr>
<td>Total</td>
<td>309/835</td>
<td>280/647</td>
<td></td>
<td>1.01</td>
<td>0.90–1.13</td>
</tr>
<tr>
<td>Chi-square</td>
<td>0.98</td>
<td></td>
<td></td>
<td>1.2</td>
<td></td>
</tr>
</tbody>
</table>

Figure 2 Clinical outcome worse or unchanged in children with upper respiratory tract infection treated with antibiotic vs. placebo.

**Favours**

---

**Favours control**

---

**Favours treatment**

---

**Favours placebo**

---

Figure 3  Subsequent complications or progression of illness in children with upper respiratory tract infection treated with antibiotic vs. placebo.

**Favours**

---

**Favours control**

---

**Favours treatment**

---

**Favours placebo**

---

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

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.17–22 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.23–26 Three of these four trials reported that antibiotic treatment had no effect on either relief of symptoms or subsequent complications in children (table 2).27 28

The quality of RCTs was variable, with a range of 4 to 10 in terms of overall quality score. The Z 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 1.7, 95% CI 0.99 to 1.13) and complications or progression of illness (relative risk 0.71, 95% CI 0.45 to 1.12) 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.17 Side effects from treatment were not significantly associated with antibiotic use (relative risk 0.8, 95% CI 0.54 to 1.21) (fig 4).

**Discussion**

This review demonstrates that antibiotic treatment of children with URTI does not alter the clinical outcome of the illness or prevent...
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. Qualitative work has demonstrated that parents of young children with acute illness were more dissatisfied when doctors provided inadequate information about the likely course of the 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.

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

<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></td>
<td></td>
</tr>
<tr>
<td>Hardy</td>
<td>4/149</td>
<td>0/88</td>
<td>1.6 4.16 [0.23,76.83]</td>
<td></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></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></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></td>
<td></td>
</tr>
<tr>
<td>Total (95%CI)</td>
<td>49/815</td>
<td>34/633</td>
<td>100.0 0.80 [0.54,1.21]</td>
<td></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.
tion concerning data from his study. This study was funded by the Royal College of General Practitioners Scientific Foundation Board.


28 Hammen RM, Hicks RJ, Bemben DA. Antibiotics and respiratory infections: are patients more satisfied when expectations are met? J Fam Pract 1996;46:56–62.


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