

**University of York Department of Health Sciences**  
**M.Sc. in Evidence Based Practice, M.Sc. in Health Services Research**  
**Exercise: Meta-analysis**

This report is from the *BMJ* (1998; **316**: 906-910). I have edited it to shorten it a bit. Read the report and then answer the questions.

**Quantitative systematic review of randomised controlled trials comparing antibiotic with placebo for acute cough in adults**

Tom Fahey, senior lecturer, <sup>a</sup> Nigel Stocks, clinical lecturer, <sup>a</sup> Toby Thomas, medical student. <sup>b</sup>

<sup>a</sup> Division of Primary Care, University of Bristol, Canynge Hall, Bristol BS8 2PR,

<sup>b</sup> United Medical and Dental Schools of Guy's and St Thomas's Hospitals, London SE11 6SP

**Abstract**

**Objectives:** To assess whether antibiotic treatment for acute cough is effective and to measure the side effects of such treatment.

**Design:** Quantitative systematic review of randomised placebo controlled trials.

**Data sources:** Nine trials (8 published, 1 unpublished) retrieved from a systematic search (electronic databases, contact with authors, contact with drug manufacturers, reference lists); no restriction on language.

**Main outcome measures:** Proportion of subjects with productive cough at follow up (7-11 days after consultation with general practitioner); proportion of subjects who had not improved clinically at follow up; proportion of subjects who reported side effects from taking antibiotic or placebo.

**Results:** Eight trials contributed to the meta-analysis. Resolution of cough was not affected by antibiotic treatment (relative risk 0.85 (95% confidence interval 0.73 to 1.00)), neither was clinical improvement at re-examination (relative risk 0.62 (0.36 to 1.09)). The side effects of antibiotic were more common in the antibiotic group when compared to placebo (relative risk 1.51 (0.86 to 2.64)).

**Conclusions:** Treatment with antibiotic does not affect the resolution of cough or alter the course of illness. The benefits of antibiotic treatment are marginal for most patients with acute cough and may be outweighed by the side effects of treatment.

**Introduction**

Acute cough and respiratory tract infection are terms used to describe a wide variety of clinical syndromes. Symptoms range from cough without sputum to an illness characterised by expectoration of mucopurulent sputum, fever, general malaise, and dyspnoea,<sup>1</sup> but coughing is nearly always present.<sup>1-4</sup> Therefore, although the terms acute bronchitis, upper respiratory tract infection, common cold, and chest infection are used in a clinical context to define separate disease entities, they represent a range of respiratory tract infection whose symptoms, causative agents, and resolution vary.<sup>1,2</sup>

Concern about the treatment of acute cough with antibiotics is not new.<sup>14 15</sup> Review articles have questioned the value of antibiotic treatment for acute bronchitis and related conditions.<sup>1 16-19</sup> To our knowledge, the absolute risk of illness without antibiotic treatment, the likely benefits and risks of treatment, and the balance of risk and benefit for individual patients have not been measured. We therefore carried out a systematic review of randomised controlled trials to establish whether antibiotics are effective in the treatment of acute cough in the community.

## Methods

### Inclusion and exclusion criteria

We included studies of patients aged greater than 12 years who were attending a family practice clinic, community based outpatient department, or an outpatient department attached to a hospital. We included patients who complained of acute cough with or without purulent sputum that had not been treated in the preceding week with antibiotic. Patients with chronic obstructive airways disease were excluded. The included studies were prospective trials in which antibiotic was allocated by formal randomisation or by quasi-randomisation, such as alternate allocation to treatment and placebo groups. Only placebo controlled trials were included; comparative studies between different classes of antibiotics were excluded. Categorical and continuous outcomes were reported in the randomised controlled trials identified at the start of the review.<sup>20-28</sup> Many different outcomes were reported in individual randomised controlled trials; we concentrated on the three most commonly reported outcomes: the proportion of subjects reporting productive cough, the proportion of subjects who had not improved clinically at re-examination, and the proportion of subjects who reported side effects from taking antibiotic or placebo.

### Systematic search

We searched Medline and EMBASE databases from 1966 and 1982 respectively using the recommended Cochrane Collaboration search strategy<sup>29</sup> and the medical subject heading (MeSH) terms "cough," "bronchitis," "sputum," and "respiratory tract infections." The search was not restricted to the English language. We also searched for references from published research by using the 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<sup>30</sup> with the search terms "bronchitis," "chest infection," and "common cold." We contacted authors of published trials requesting knowledge of any unpublished studies. We also wrote to drug companies in the United Kingdom that manufacture antibiotics (as given in the British National Formulary) requesting unpublished trials.

## Analysis

Because the events in the treatment and control arms occurred frequently, significance and clinical importance were evaluated by estimating relative risk.<sup>32</sup> As the inclusion criteria and event rates reported in the control arms varied, the pooled relative risks were estimated with 95% confidence intervals by means of both random effects and fixed effects models.<sup>34</sup> Antibiotic is significantly better than placebo in improving a condition when the upper limit of the 95% confidence interval is <1. Conversely, side effects of antibiotic treatment are significant when the lower 95% confidence limit of the relative risk is >1.

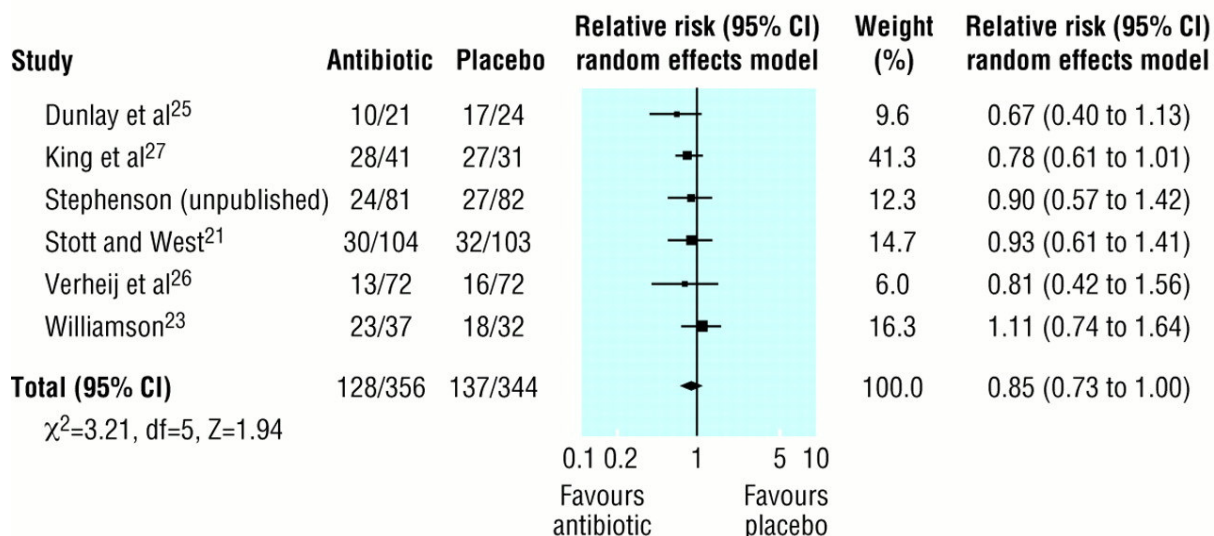
## Results

### Trials found

Our search uncovered nine trials that met the inclusion criteria for this review (M Stephenson, unpublished data).<sup>21-28</sup> The losses to follow up, antibiotic regimen, outcome measured, recommendation for antibiotic treatment, and characteristics of patients for these nine trials are available as two tables on the *BMJ's* website ([www.bmj.com](http://www.bmj.com)).

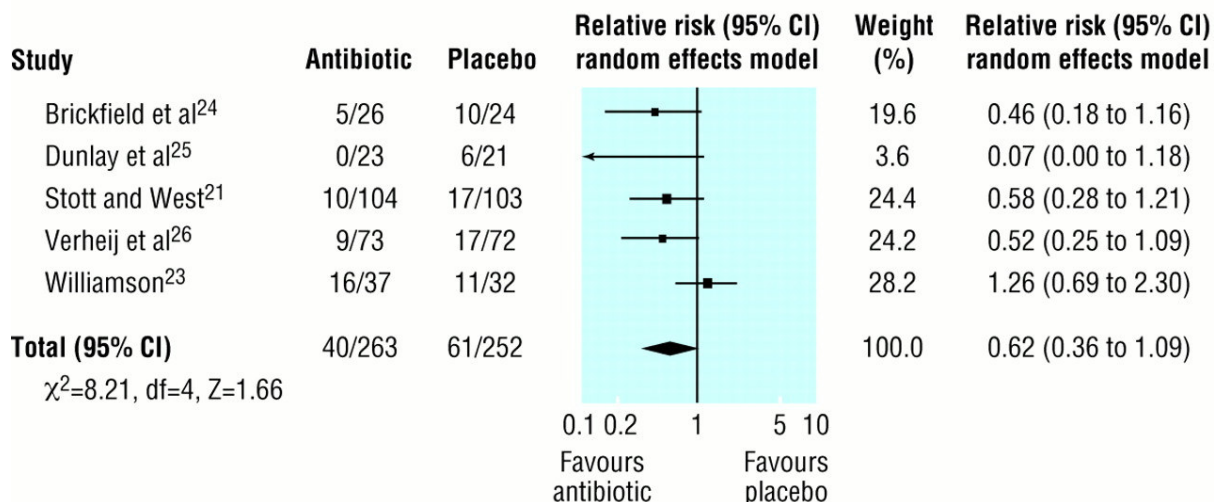
We excluded Howie and Clark's trial from the 1970s in 829 patients.<sup>20</sup> Although the unit of randomisation was patients who were instructed to take either antibiotic or placebo at the start of a respiratory illness, the unit of analysis was episodes of illness. Some patients did not contribute any episodes of illness to the analysis (198/829 participants, or 24% of those randomised) while others reported more than one episode of illness (1.52 and 1.55 courses in the antibiotic and placebo arms respectively).<sup>20</sup> This trial reported no difference between antibiotic and placebo in all outcomes reported at the end of the trial. One other unpublished trial that had reported no difference in outcome between antibiotic and placebo in 33 patients,<sup>36</sup> had no original data remaining (S Thomas,

**Proportion of subjects with productive cough at follow up**



**Fig 2. Comparison of antibiotic and placebo treatment on resolution of productive cough at days 7-11**

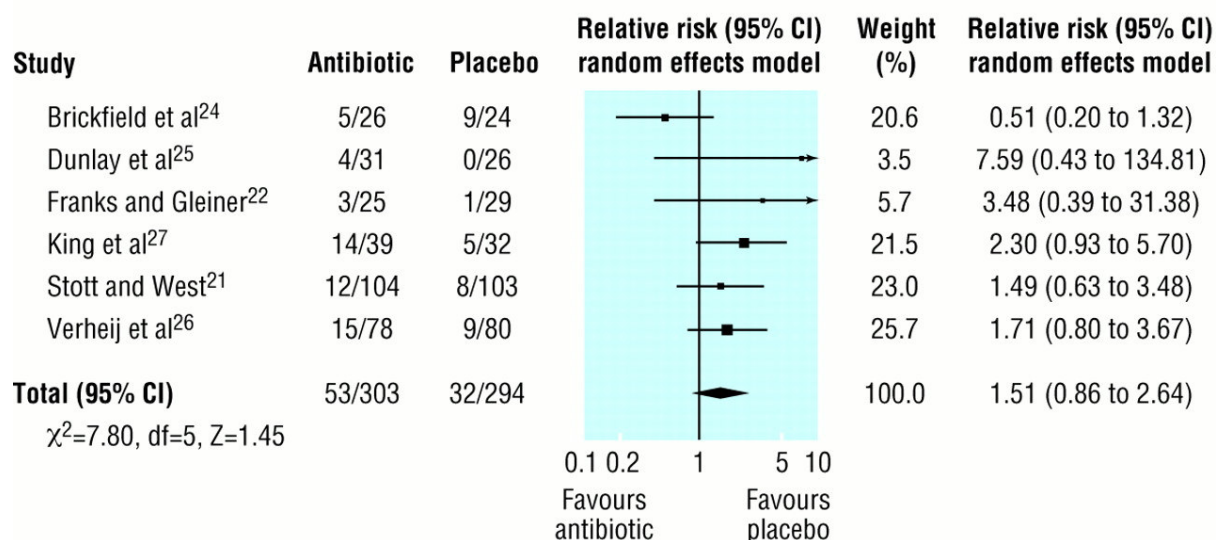
**Proportion of subjects who had not improved clinically at follow up**



**Fig 3. Comparison of antibiotic and placebo treatment on clinical improvement at days 7-11**

personal communication). Franks and Gleiner reported the average percentage of days with cough over a period of seven days (all subjects in placebo arm, 92% of subjects in antibiotic arm) but not the number of patients with cough at a specified end point.<sup>22</sup> No further data were available (P Franks, personal communication), so this trial contributed data to the part of the meta-analysis which examined the side effects of treatment only. King *et al.* included patients aged 8 years and over, but the average age of participants was 37 years and so we included this trial.<sup>27</sup> Finally, one trial by Scherl *et al.* did not contribute data to the meta-analysis because it reported on a continuous variable, the mean number of days with cough.<sup>28</sup> No additional information could be obtained because the author of the report had died. This left us with a total of eight trials reporting on the three specified outcome measures.

### Proportion of subjects with side effects



**Fig 4. Comparison of antibiotic and placebo treatment on rate of reporting of side effects**

### Efficacy of antibiotic

Antibiotic treatment was no better than placebo when the resolution of cough at days 7-11 was assessed (relative risk 0.85 (95% confidence interval 0.73 to 1.00)) (fig 2). Similarly, when the proportion of subjects who had not improved clinically was assessed at days 7-11 in five trials antibiotic treatment did not significantly improve the resolution of illness (relative risk 0.62 (0.36 to 1.09)) (fig 3).<sup>21 23-26</sup>

### Side effects of treatment

The mean percentage of subjects reporting side effects from antibiotic treatment in seven trials was 19% (range 12% to 36%). In all but one trial<sup>24</sup> the percentage of subjects reporting side effects was higher in the antibiotic arm; subsequent pooling of data showed that a course of antibiotic was associated with a non-significant increase in the risk of side effects from antibiotic (relative risk 1.51 (0.86 to 2.64)) (fig 4). When the one trial which reported an increase in side effects from placebo was excluded,<sup>24</sup> the heterogeneity between trials was reduced and side effects were significantly associated with antibiotic use (relative risk 1.9 (1.19 to 3.02), 2 test for heterogeneity=1.73,  $df=4$ ,  $P>0.5$ ).

### Discussion

This systematic review shows that antibiotic treatment has no effect on the resolution of acute cough. For both measures of efficacy the proportion of subjects coughing and the proportion whose symptoms had not improved at days 7-11 antibiotic was no different from placebo. Furthermore, treatment with antibiotic may incur side effects in a few patients.

### Shortcomings

This review has several shortcomings. Firstly, the outcomes chosen and assessed in each of the randomised trials were varied and different. Consequently, when the results were pooled several important outcomes were reported only in some of the trials and were measured in different ways. For example, time off work was measured as a continuous outcome in two trials,<sup>23 28</sup> as a categorical outcome in three others,<sup>21 22 25</sup> as a categorical and continuous outcome in one trial,<sup>27</sup> and not at all in the remaining trials (M Stephenson, unpublished data).<sup>24 26</sup>

Secondly, more recent generic scores for measuring the quality of life were not used in any of the trials, once again limiting the propensity to combine the results. Therefore important information for patients such as the effect of antibiotic on quality of life and on return to work is not reported.

Finally, the timing of assessment differed between trials. Such differences make it difficult to measure the clinical course of acute cough. These shortcomings reflect the difficulty in combining results from pragmatic randomised trials that examine outcomes based on illness in general practice. Nevertheless, substantially important differences between antibiotic and placebo are unlikely to be present in these other outcomes: individual trials did not report any substantial benefit of antibiotic in the outcomes that we did not consider in this systematic review.

### **Conclusions**

This systematic review shows that antibiotic is unlikely to alter the course of illness in most adult patients presenting with acute cough. A minority may have side effects from treatment. When managing individual patients the potential risks from treatment including side effects, costs of antibiotic, alteration in consulting behaviour, and increased bacterial resistance should all be considered before initiating treatment.

### **QUESTIONS ABOUT THIS REPORT:**

- (a) What kind of study is this?
- (b) In the summary we read 'Resolution of cough was not affected by antibiotic treatment (relative risk 0.85 (95% confidence interval 0.73 to 1.00)),' What is a relative risk? What does the 95% confidence interval tell us?
- (c) Why do the authors say that resolution of cough was not affected? Do you agree with this interpretation?
- (d) What kind of graphs are shown in the figures?
- (e) In the figures, what kind of scale is used for the relative risks? Why are these scales used here?
- (f) In the figures, what do the squares and the horizontal lines represent?
- (g) In the figures, what do the diamond or lozenge shapes represent?
- (h) Do you think the diamonds are drawn correctly?
- (i) In the analysis of side effects of treatment, the authors say: 'When the one trial which reported an increase in side effects from placebo was excluded, the heterogeneity between trials was reduced and side effects were significantly associated with antibiotic use'. What does 'heterogeneity' mean here? Do you think the author's approach is reasonable?
- (j) What are the main conclusions as whether antibiotics should be used in the treatment of acute cough? Are they justified by the data?