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

Division of Primary Care, University of Bristol, Canynge Hall, Whiteladies Road, Bristol BS8 2PR, UK
T Fahey
N Stocks

United Medical and Dental Schools, London SE11 6SP, UK
T Thomas
Toby Thomas died in a road traffic accident on 26 November 1996.

Correspondence to:
Dr Fahey.
email: tom.fahey@bris.ac.uk

Accepted 9 April 1998

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.[1] 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.[2] 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.[3]

Despite the predominantly viral cause, antibiotics are frequently prescribed to children with symptoms of URTI.[4] 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.[4] 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.[5 6]

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 a 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.[7] 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

Trial	*Year published*	*Number of participants*	*Age of children*	*Setting*	*Diagnostic label*	*Clinical features*
Hardy[17]	1956	217 randomised, 118 male, 99 female; 149 analysed (68.7% follow up)	0 to 13 years	Outpatient clinic	Uncomplicated respiratory infections	Fever ⩾ 38°C Negative clinical examination except for nasopharyngitis
Townsend[24]	1960	845 children (total number of cases seen in 1884)	2 months to 12 years	Private US paediatric practice	Suspected viral respiratory infection	Not reported
Wynn-Williams[25]	1961	96 children	2 to 12 years	Community setting in UK	Families selected and then randomised from children with "past history of frequent colds going onto the chest". Initiation of treatment if mother suspected URI in child "severe enough to put child to bed or prevent attendance at school"	Not reported
Townsend[23]	1962	781 children	0 to 12 years	Private US paediatric practice	Children with a "febrile respiratory illness"	All "presented signs and symptoms of the respiratory system". Cases further classified into measles, croup, and others
Ackerman[18]	1968	60 children	3 to 12 months	US army dispensary	Undifferentiated respiratory infection	Acute change in state of health Undifferentiated symptoms of URI Rectal temperature > 38°C
Lexomboon[19]	1971	174 children	6 months to 12 years (half < 2 years)	Outpatient department hospital in Thailand	Upper respiratory infection	Fever ⩾ 39°C Symptoms of RTI < 48 h
Gordon[26]	1974	89 children	< 2 years to 6 years	A & E department in children's hospital, Australia	Minor respiratory illness	Symptoms referable to respiratory tract, most had cough and running nose, no antibiotic in previous week
Taylor[20]	1977	197 children	2 to 10 years	Suburban general practice in New Zealand	Presumed viral respiratory infections	Classified as having nasopharyngitis (42), pharyngo-tonsillitis (71), bronchitis or laryngotracheo-bronchitis (84)
Todd[21]	1984	142 children	> 2 months; mean (SD) 2 (2) years	2 paediatric offices and 1 clinic in army base in US	Purulent nasopharyngitis	All had purulent nasal discharge with or without other signs of respiratory illness
Sutrisna[22]	1991	900 children	< 5 years; 38% (antibiotic) 35% (placebo) were infants	Health clinics in Indonesia	Mild acute respiratory infection	Mild acute respiratory infection defined according to WHO criteria: mild upper respiratory signs such as cough, runny nose and/or fever (>37°C) Respiratory rate < 50/min
Darelid[15]*	1993	88 children	6 months to 6 years	3 paediatric outpatient departments in Sweden	Longstanding *Moraxella catarrhalis* associated cough	Persistent cough > 10 days seeking medical help. Excluded clinically suspected pertussis (known exposure or whooping)
Gottfarb[16]*	1994	37 children	7 months to 7 years	3 paediatric outpatient departments in Sweden	Persistent cough	Lower respiratory infection with cough for a minimum of 10 days. Children with frequent cough, ⩾ 11 coughing attacks/24 h were included

*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,[8] 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,[9] 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*.[10] 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

Table 2 Interventions, outcomes, and quality of trials

Trial	*Antibiotic dosage*	*Antibiotic duration*	*Outcomes measured*	*Contribution to meta-analysis*	*Quality*	*Favours antibiotic?*
Hardy[17]	Gantrisin, penicillin or aureomycin, dosage not stated but antibiotic given "adjusting the dosage according to a predetermined scale, based on weight and age". Given qid	4 days	Complication rate in a two week period	Yes, outcome 2	7	No
Townsend[24]	Sulphonamides 0.1 g/kg/24 h Tetracyclines 40–50 mg/kg/24 h Another group of children randomised to "prophylactic" treatment, of same drugs at "approximately ¼ of the therapeutic dose".	Not stated	Complication rate	No	4	No
Wynn-Williams[25]	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	2 days	Subsequent URIs (measured as episodes) Average duration of symptoms	No	7	Yes
Townsend[23]	Sulphonamides (0.5 g per teaspoonful) Tetracycline (125 mg per teaspoonful) Chloramphenicol (125 mg per teaspoonful) Penicillin (200000 units per teaspoonful) All given by a dosage schedule	For as long as child was febrile	Not given	No	6	No
Ackerman[18]	Penicillin V (100000 units qid) Tetracycline 50 mg qid)	10 days	Clinical state at follow up (48 h) Progression of initial symptoms Mean duration of respiratory morbidity Continuous respiratory symptoms (day 7) "Complications" (side effects)	Yes, outcome 1, 2, and 3	10	No
Lexomboon[19]	Penicillin 30 mg/kg/day Tetracycline 40 mg/kg/day	7 days	Clinical outcome (day 7)	Yes, outcome 1	7	No
Gordon[26]	Penicillin Ampicillin Erythromycin Dosage 125 mg/5 ml Age < 2 years: 3 to 5 ml qid Older children: 5 to 10 ml qid	Not stated	Relief of symptoms Improvement of physical signs	No	5	No
Taylor[20]	Amoxycillin (125 ml/5 ml) Co-trimoxazole (sulphamethoxazole 200 mg and trimethoprim 40 mg/5 ml)	5 days	Treatment failure Symptoms at day 8 Not returned to normal activity day 8 Side effects	Yes, outcomes 1, 2, and 3	8	Yes (treatment failure) No (other outcomes)
Todd[21]	Cephalexin 25–50 mg/kg/day	5 to 6 days	Assessed at day 5 to 6 Parent assessed: drug benefit drug side effects Physician assessed: fever nasal discharge complications	Yes, outcomes 1, 2, and 3	9	No
Sutrisna[22]	Ampicillin (25–30 mg/kg) qid	5 days	Clinical outcome at 5–7 and 14 days Side effects	Yes, outcomes 1 and 3	7	No
Darelid[15]*	Erythromycin suspension 50 mg/kg/day	7 days	Cough at 7 days Worsening cough, fever and purulent sputum Side effects	No	8	Yes, but open trial, parent and investigator knew treatment assignment
Gottfarb[16]*	Amoxycillin/clavulanic acid 20 mg/kg/day	7 days	Number of coughing attacks each day for 8 days Clinical improvement judged by parents day 12 Clinical improvement judged by doctor day 12	No	6	Yes

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.

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.[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 REVMAN 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

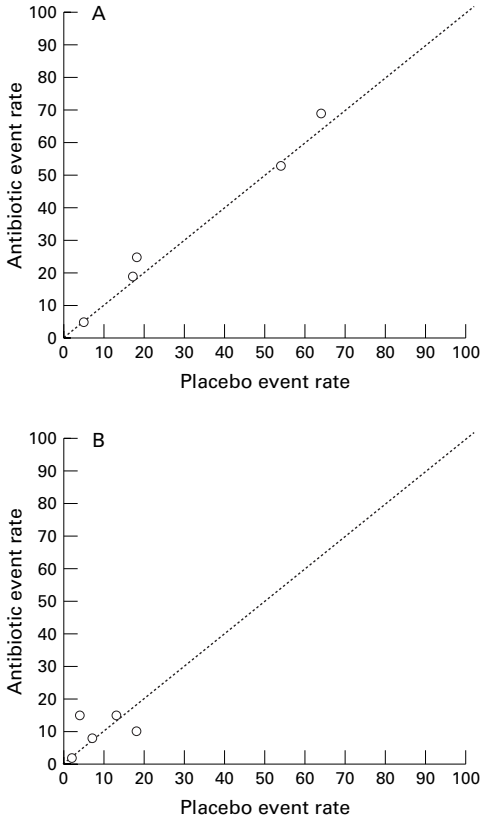

Figure 1 L'Abbe plots of the proportion of children in whom (A) the clinical outcome was worse or unchanged and (B) who suffered complications or progression of illness.

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]

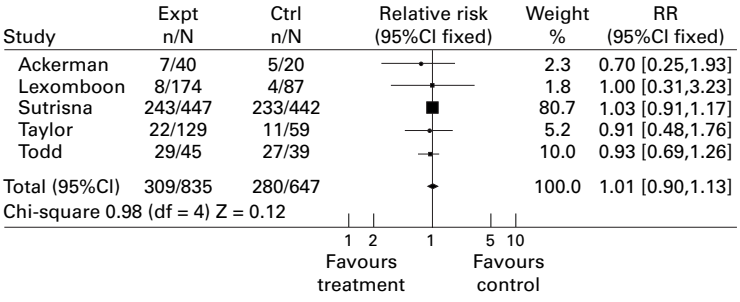

Figure 2 Clinical outcome worse or unchanged in children with upper respiratory tract infection treated with antibiotic v placebo.

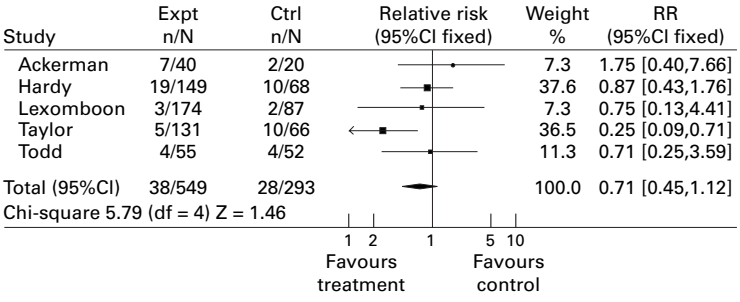

Figure 3 Subsequent complications or progression of illness in children with upper respiratory tract infection treated with antibiotic v placebo.

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).[23 24 26]

The quality of RCTs was variable, with a range of 4 to 10 in terms of overall quality score. The κ 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 1.01, 95% CI 0.90 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

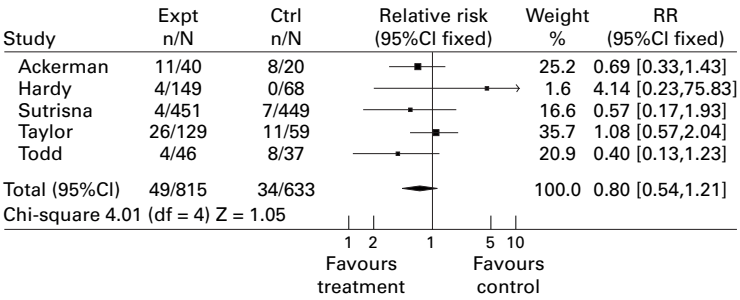

Figure 4 Side effects of treatment in children with upper respiratory tract infection treated with antibiotic v placebo.

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.[5 6] Observational research in a cohort of 965 children in UK general practice[4] 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*,[22] 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.[27] 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.[23–26] Only one of these trials reported a positive effect of antibiotic treatment.[25] Lastly, two trials reported a beneficial effect of antibiotic treatment but were not included in the pooled analysis in this review.[15 16] 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.[28] Patients with URTI are more satisfied when doctors explain the nature of likely course of their illness.[28] 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.[29] 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.[30]

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.[4] 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.[31] 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.[32 33] These considerations emphasise that antibiotic treatment is not a risk free policy[34]; careful measurement of the likely benefit and harm of treatment is required for all cases of URTI.[35]

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 clarifica-

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

1 Royal College of General Practitioners OPCS and Department of Health. *Morbidity statistics from general practice*. Fourth national study, 1991–1992. London: HMSO, 1995.
2 Gwaltney JM. The common cold. In: Mandell GL, Bennet JE, Dolin R, eds. *Principles and practice of infectious disease*. 4th ed. New York: Churchill Livingstone, 1995:561–6.
3 Turner RB, Lande AE, Chase P, Hilton N, Weinberg D. Pneumonia in pediatric outpatients: cause and clinical manifestations. *J Pediatr* 1987;**111**:194–200.
4 Stott N. Management and outcome of winter upper respiratory tract infections in children aged 0–9 years. *BMJ* 1979; i:29–31.
5 Davis SD, Wedgwood RJ. Antibiotic prophylaxis in acute viral respiratory diseases. *Am J Dis Child* 1965;**109**:544–53.
6 Soyka LF, Robinson DS, Lachant N, Monaco J. The misuse of antibiotics for treatment of upper respiratory tract infections in children. *Pediatrics* 1975;**55**:552–6.
7 World Organisation of National Colleges and Academies of General Practice. *An international classification of health problems of primary health care (ICHPPC-2)*. 3rd ed. Oxford: Oxford University Press, 1983.
8 Dickerson K, Scherer R, Lefebvre C. Identifying relevent studies for systematic reviews. In: Chalmers I, Altman D, eds. *Systematic reviews*. London: BMJ Publishing Group, 1995:17–36.
9 Cochrane Collaboration. *The Cochrane library*. v. Issue 2. Oxford: Update Software, 1997.
10 Mulrow CD, Oxman AD. Cochrane collaboration handbook (updated 9 December 1996). In: The Cochrane Collaboration, ed. *The Cochrane library*. Issue 2. Oxford: Update Software, 1996.
11 Hennekens C, Buring J. *Epidemiology in medicine*. Boston: Little Brown and Co, 1987.
12 L'Abbe KA, Detsky AS, O'Rourke K. Meta-analysis in clinical research. *Ann Intern Med* 1987;**107**:224–33.
13 Petitti DB. Meta-analysis, decision analysis and cost-effectiveness analysis. *Methods for quantitative synthesis in medicine*. New York: Oxford University Press, 1994.
14 Eichenwald HF, Perry HC. Unpublished trial. Cited in pediatric conference. *Arch Pediatrics* 1960;**77**:171–87.
15 Darelid J, Lofgren S, Malmvall B. Erythromycin treatment is beneficial for longstanding Moraxella catarrhalis associated cough in children. *Scand J Infect Dis* 1993;**25**:323–9.
16 Gottfarb P, Brauner A. Children with persistent cough—outcome with treatment and role of Moraxella catarrhalis? *Scand J Infect Dis* 1994;**26**:545–51.
17 Hardy LM, Traisman HS. Antibiotics and chemotherapeutic agents in the treatment of uncomplicated respiratory infections in children. *J Pediatr* 1956;**48**:146–56.
18 Ackerman B. Treatment of undifferentiated respiratory infections in infants. *Clin Pediatr* 1968;**7**:391–5.
19 Lexomboon U, Duangmani C, Kusalasai V, Sunakorn P, Olson LC, Noyes HE. Evaluation of orally administered antibiotics for treatment of upper respiratory infections in Thai children. *J Pediatr* 1971;**78**:772–8.
20 Taylor B, Abbott GD, Kerr MMcK, Fergusson DM. Amoxycillin and co-trimoxazole in presumed viral respiratory infections of childhood:placebo-controlled trial. *BMJ* 1977;ii:552–4.
21 Todd JK, Todd N, Damato J, Todd W. Bacteriology and treatment of purulent nasopharyngitis: a double blind, placebo-controlled evaluation. *Pediatr Infect Dis J* 1984;**3**: 226–32.
22 Sutrisna B, Frerichs RR, Reingold AL. Randomised controlled trial of effectiveness of ampicillin in mild acute repiratory infections in Indonesian children. *Lancet* 1991; **338**:471–4.
23 Townsend EH, Radebaugh JF. Prevention of complications of respiratory illnesses in pediatric practice. *N Engl J Med* 1962;**266**:683–9.
24 Townsend EH. Chemoprophylaxis during respiratory infection in private practice. *Am J Dis Child* 1960;**34**:566–73.
25 Wynn-Williams N. Control of respiratory infections in children by tetracycline. *BMJ* 1961;i:469–70.
26 Gordon M, Lovell S, Dugdale A. The value of antibiotics in minor respiratory illness in children. *Med J Aust* 1974;**1**: 304–6.
27 Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple graphical test. *BMJ* 1997;**315**:629–934.
28 Hamm RM, Hicks RJ, Bemben DA. Antibiotics and respiratory infections:are patients more satisfied when expectations are met? *J Fam Pract* 1996;**43**:56–62.
29 Kai J. Parents' difficulties and information needs in coping with acute illness in preschool children: a qualitative study. *BMJ* 1996;**313**:987–90.
30 Froom J, Culpepper L, Jacobs M, *et al*. Antimicrobials for acute otitis media? A review fromt the International Primary Care Network. *BMJ* 1997;**315**:98–102.
31 Little P, Gould C, Williamson I, Warner G, Gantley M, Kinmonth AL. Reattendance and complications in a randomised trial of prescribing strategies for sore throat: the medicalising effect of prescribing antibiotics. *BMJ* 1997;**315**:350–2.
32 Davey PG, Bax RP, Newey J, *et al*. Growth in the use of antibiotics in the community in England and Scotland in 1980–93. *BMJ* 1996;**312**:613.
33 Arason VA, Kristinsson KG, Sigurdsson JA, Stefánsdóttir G, Mölstad S, Gudmundsson S. Do antimicrobials increase the carriage rate of penicillin resistant pneumococci in children? Cross sectional prevalence study. *BMJ* 1996;**313**: 387–91.
34 Orton P. Resistant organisms: a dilemma for primary care? *Br J Gen Pract* 1997;**47**:415–16.
35 Gilbert R, Logan S. Future prospects for evidence-based child health. *Arch Dis Child* 1996;**75**:465–8.