RCSI

Royal College of Surgeons in Ireland
e-publications@RCSI

General Practice Articles | Department of General Practice

1-3-2014

Antibiotics for acute bronchitis.

Susan M. Smith
Royal College of Surgeons in Ireland

Tom Fahey
Royal College of Surgeons in Ireland

John Smucny
Palo Alto Medical Foundation, Dublin Center, Dublin, California, USA

Lorne A. Becker
Department of Family Medicine, SUNY Upstate Medical University

Citation

Smith SM, Fahey T, Smucny J, Becker LA. Antibiotics for acute bronchitis. Cochrane Database of Systematic Reviews. 2014 Mar 1;3:CD000245. doi: 10.1002/14651858.CD000245.pub3. (http://dx.doi.org/10.1002/14651858.CD000245.pub3)

This Article is brought to you for free and open access by the Department of General Practice at e-publications@RCSI. It has been accepted for inclusion in General Practice Articles by an authorized administrator of e-publications@RCSI. For more information, please contact epubs@rcsi.ie.

RCSI

— Use Licence —

Attribution-Non-Commercial-ShareAlike 1.0
You are free:
• to copy, distribute, display, and perform the work.
• to make derivative works.
Under the following conditions:
• Attribution — You must give the original author credit.
• Non-Commercial — You may not use this work for commercial purposes.
• Share Alike — If you alter, transform, or build upon this work, you may distribute the resulting work only under a licence identical to this one.
For any reuse or distribution, you must make clear to others the licence terms of this work. Any of these conditions can be waived if you get permission from the author.
Your fair use and other rights are in no way affected by the above.

This work is licenced under the Creative Commons Attribution-Non-Commercial-ShareAlike License. To view a copy of this licence, visit:
URL (human-readable summary):
• http://creativecommons.org/licenses/by-nc-sa/1.0/
URL (legal code):
• http://creativecommons.org/worldwide/uk/translated-license

This article is available at e-publications@RCSI: http://epubs.rcsi.ie/gpart/55

Antibiotics for acute bronchitis (Review)

Smith SM, Fahey T, Smucny J, Becker LA

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2014, Issue 3

http://www.thecochranelibrary.com

WILEY

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

TABLE OF CONTENTS

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

[Intervention Review]

Antibiotics for acute bronchitis

Susan M Smith[1], Tom Fahey[2], John Smucny[3], Lorne A Becker[4]

[1]Department of General Practice, Royal College of Surgeons, Dublin, Ireland. [2]Department of Family Medicine and General Practice, Royal College of Surgeons in Ireland Medical School, Dublin, Ireland. [3]Palo Alto Medical Foundation, Dublin Center, Dublin, California, USA. [4]Department of Family Medicine, SUNY Upstate Medical University, Syracuse, New York, USA

Contact address: Susan M Smith, Department of General Practice, Royal College of Surgeons, Beaux Lane House, Mercer St, Dublin, 2, Ireland. susansmith@rcsi.ie. susmarsmith@gmail.com.

Editorial group: Cochrane Acute Respiratory Infections Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 3, 2014.
Review content assessed as up-to-date: 15 January 2014.

Citation: Smith SM, Fahey T, Smucny J, Becker LA. Antibiotics for acute bronchitis. *Cochrane Database of Systematic Reviews* 2014, Issue 3. Art. No.: CD000245. DOI: 10.1002/14651858.CD000245.pub3.

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ABSTRACT

Background

The benefits and risks of antibiotics for acute bronchitis remain unclear despite it being one of the most common illnesses seen in primary care.

Objectives

To assess the effects of antibiotics in improving outcomes and assess adverse effects of antibiotic therapy for patients with a clinical diagnosis of acute bronchitis.

Search methods

We searched CENTRAL 2013, Issue 12, MEDLINE (1966 to January week 1, 2014), EMBASE (1974 to January 2014) and LILACS (1982 to January 2014).

Selection criteria

Randomised controlled trials (RCTs) comparing any antibiotic therapy with placebo or no treatment in acute bronchitis or acute productive cough, in patients without underlying pulmonary disease.

Data collection and analysis

At least two review authors extracted data and assessed trial quality.

Main results

Seventeen trials with 3936 participants were included in the primary analysis. The quality of trials was generally good. There was limited evidence to support the use of antibiotics in acute bronchitis. At follow-up, there was no difference in participants described as being clinically improved between antibiotic and placebo groups (11 studies with 3841 participants, risk ratio (RR) 1.07, 95% confidence interval (CI) 0.99 to 1.15; number needed to treat for an additional beneficial outcome (NNTB) 22. Participants given antibiotics were less likely to have a cough (four studies with 275 participants, RR 0.64, 95% CI 0.49 to 0.85; NNTB 6); have a night cough (four studies with 538 participants, RR 0.67, 95% CI 0.54 to 0.83; NNTB 7) and a shorter mean cough duration (seven studies with 2776 participants, mean difference (MD) -0.46 days, 95% CI -0.87 to -0.04). The differences in presence of a productive cough at follow-up and MD of productive cough did not reach statistical significance.

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Antibiotic-treated patients were more likely to be unimproved according to clinician's global assessment (six studies with 891 participants, RR 0.61, 95% CI 0.48 to 0.79; NNTB 25); have an abnormal lung exam (five studies with 613 participants, RR 0.54, 95% CI 0.41 to 0.70; NNTB 6); have a reduction in days feeling ill (five studies with 809 participants, MD -0.64 days, 95% CI -1.16 to -0.13) and a reduction in days with limited activity (six studies with 767 participants MD -0.49 days, 95% CI -0.94 to -0.04). The differences in proportions with activity limitations at follow-up did not reach statistical significance. There was a significant trend towards an increase in adverse effects in the antibiotic group (12 studies with 3496 participants) (RR 1.20, 95% CI 1.05 to 1.36; NNT for an additional adverse effect 5).

Authors' conclusions

There is limited evidence to support the use of antibiotics in acute bronchitis. Antibiotics may have a modest beneficial effect in some patients such as frail, elderly people with multimorbidity who may not have been included in trials to date. However, the magnitude of this benefit needs to be considered in the broader context of potential side effects, medicalisation for a self-limiting condition, increased resistance to respiratory pathogens and cost of antibiotic treatment.

PLAIN LANGUAGE SUMMARY

Antibiotic treatment for people with a clinical diagnosis of acute bronchitis

Acute bronchitis is a clinical diagnosis for an acute cough, which may or may not be productive of mucus or sputum. It occurs when the tubes (bronchi) within the lungs become inflamed and may be caused by viruses or bacteria. Symptoms generally last for two weeks but the associated cough can last for up to eight weeks. Recently, there has been controversy over the term acute bronchitis as it covers a range of clinical presentations that may overlap with other diagnoses such as upper or lower respiratory tract infections. For this reason, some have suggested using the term 'acute lower respiratory tract infection when pneumonia is not suspected' as this is more specific. Antibiotics are commonly prescribed to treat this condition though other treatments providing symptom relief are commonly used. Antibiotics can have adverse effects such as nausea and diarrhea but can cause more serious reactions related to anaphylaxis in those allergic to them. In healthy communities, there is little evidence of bacterial infection in people with bronchitis and there is no practical test to distinguish between bacterial and viral bronchitis. Within this context the use of antibiotics to treat acute bronchitis is controversial but common. Concerns that prescribing unnecessary antibiotics increases antibiotic resistance exists.

We included 17 trials with 3936 participants diagnosed with acute bronchitis and randomly assigned to receive any antibiotic treatment or a placebo or no treatment. Co-treatments with other medications to relieve symptoms were allowed if they were given to all patients. We excluded patients with pre-existing underlying pulmonary disease such as chronic bronchitis or chronic obstructive pulmonary disease. The quality of trials was generally good, particularly for more recent studies. There was limited evidence to support the use of antibiotics for acute bronchitis and a large study involving 1038 patients from 12 countries included in this update has confirmed this finding. Some people treated with antibiotics recovered a bit more quickly with reductions in cough-related outcomes though the difference was of doubtful clinical significance as it amounted to a difference of half a day over an 8 to 10 day period. There was a statistically significant but small increase in adverse side effects in patients treated with antibiotics. The most commonly reported side effects included nausea, vomiting or diarrhea, headaches, skin rash and vaginitis.The available evidence suggests that there is no benefit in using antibiotics for acute bronchitis in otherwise healthy individuals though more research is needed on the effect in frail, elderly people with multimorbidities who may not have been included in the existing trials. The use of antibiotics needs to be considered in the context of the potential side effects, medicalisation for a self-limiting condition and costs of antibiotic use, particularly the potential harms at population level associated with increasing antibiotic resistance.

BACKGROUND

Description of the condition

Acute bronchitis is a common illness which is characterised by fever and cough that is often wheezy in nature and the cough

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

may or may not be productive. Acute bronchitis occurs when the bronchi become inflamed and it may be caused by either viral or bacterial infection. Symptoms generally last for two weeks but the associated cough can last for up to eight weeks (CDC 2013). It is the ninth most common among outpatient illnesses recorded by physicians in ambulatory practice in the USA (Delozier 1989) and the fifth most commonly encountered by Australian General Practitioners, for whom it represents 3.5% of encounters and 2.4% of problems seen (Meza 1994). In the UK, there are 300 to 400 consultations for treatment of respiratory tract infections per 1000 registered patients each year and while antibiotic prescribing for these conditions had declined between 1995 and 2000, it has since stabilised (Gulliford 2011). The European Centre for Disease Prevention and Control provides data on trends in antimicrobial consumption across Europe suggesting that overall antibiotic use varies across Europe with most countries showing increases over the period 1997 to 2010 (ECDC 2013).

Population-based estimates of the incidence of acute bronchitis range from 33 to 45 cases per 1000 per year (Ayres 1986; Mainous 1996). Patients with bronchitis miss an average of two to three days off work per episode. The great majority of episodes of acute bronchitis in healthy individuals are presumed to be viral infections, although this has been questioned (Macfarlane 1994). Community-based studies have isolated viruses in 8% to 23% of cases (Boldy 1990; Macfarlane 1993; Stuart-Harris 1965). Other pathogens implicated in acute bronchitis are *Mycoplasma pneumoniae (M. pneumoniae)*, *Chlamydia pneumoniae* (*C. pneumoniae)* and *Bordetella pertussis* (*B. pertussis)*, each of which has been identified in up to 25% of cases in various populations (Boldy 1990; Falck 1994; Foy 1993; Grayston 1993; Herwaldt 1991; Jonsson 1997; King 1996; Macfarlane 1993; Robertson 1987; Stuart-Harris 1965; Thom 1994). A more recent study assessing the aetiology and outcome of acute lower respiratory tract infection in 638 adults in UK primary care, showed that in 55% viral or bacterial pathogens were identified (Macfarlane 2001).

Description of the intervention

The use of antibiotics for patients with acute bronchial infections remains a controversial area in primary health care practice (Coenen 2007; Gonzales 1995). *Streptococcus pneumoniae* (*S. pneumoniae), Haemophilus influenzae (H. influenza)* and*Moraxella catarrhalis (M. catarrhalis)* have been isolated from sputum samples in up to 45% of patients with acute bronchitis (Henry 1995; Macfarlane 1993) but their role is difficult to assess because of potential oropharyngeal colonisation in healthy individuals (Laurenzi 1961; Smith 1986). Unfortunately, there are no clinically useful criteria that accurately help distinguish bacterial from viral bronchial infections. Therefore, some authors have called for physicians to stop prescribing antibiotics for patients with acute bronchitis (Gonzales 1995; Hueston 1997). Nonetheless, antibiotics are prescribed for 60% to 83% of patients who present to physicians with this disorder (Gonzales 1997; Mainous 1996; Meza 1994; Petersen 2007; Straand 1997). Overall antibiotic use varies across Europe with most countries showing increases over the period 1997 to 2010 (ECDC 2013).

How the intervention might work

Antibiotics may improve outcomes in acute bronchitis if the disease is caused by a bacterial infection. They have no antiviral activity so are not effective in viral bronchitis. In addition, antibiotics can cause harm relating to their adverse effect on normal bacteria colonising the intestine. These adverse effects most commonly include gastrointestinal symptoms such as nausea and diarrhea but antibiotics can also cause more serious reactions related to anaphylaxis in those allergic to them.

Why it is important to do this review

As acute bronchitis occurs so frequently, it is important to obtain some estimate of the probable effectiveness of antibiotic therapy. If effective, antibiotics could shorten the course of the disease and reduce the loss of productive work time it causes. However, any benefit from antibiotics must be weighed against the possibility that excessive antibiotic use will lead to increases in cost and patient morbidity, as well as development of resistant strains of common organisms (Coenen 2007; Molstad 1992) and unnecessary medicalisation of individuals with a self-limiting illness (Little 2005). If antibiotics are ineffective, then their use should be discontinued.

OBJECTIVES

To assess the effects of antibiotics in improving outcomes and assess adverse effects of antibiotic therapy for patients with a clinical diagnosis of acute bronchitis.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) in patients with acute bronchitis assigned to treatment with an antibiotic or a placebo or no active treatment.

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Types of participants

We included trials that included patients of either sex or any age with a clinical syndrome of cough with or without productive sputum, with a physician's diagnosis of acute bronchitis or cough with persistent cold or flu-like illness that was not resolving. The term "acute lower respiratory tract infection when pneumonia is not suspected" is also used to describe this clinical presentation. We excluded trials that included patients with pre-existing chronic bronchitis (i.e. acute exacerbation of chronic bronchitis).

Types of interventions

We included all RCTs comparing any antibiotic therapy versus no treatment or placebo in the management of acute bronchitis. We excluded trials comparing one antibiotic regimen with another, or trials comparing the use of other active medications (such as bronchodilators) with antibiotic therapy in this review. We included trials that allowed concurrent use of other medications such as analgesics, antitussives, antipyretics or mucolytics if they allowed equal access to such medications for patients in the antibiotic and control groups.

Types of outcome measures

We included the following range of cough-related and general clinical outcomes.

Primary outcomes

1. Cough-related outcomes including:
   i) time to resolution of cough;
   ii) sputum production, defined as proportion of patients with or without sputum;
   iii) proportions of patients with cough, night cough, productive cough.
2. Global assessment of improvement by clinicians at follow-up.
3. General clinical outcomes including:
   i) severity of symptoms;
   ii) activity limitations;
   iii) abnormal lung examination at a designated follow-up visit.

Secondary outcomes

1. Adverse effects.

Search methods for identification of studies

Electronic searches

For this updated review, we searched the Cochrane Central Register of Controlled Trials (CENTRAL) 2013, Issue 12, part of *The Cochrane Library,* www.thecochranelibrary.com (accessed 15 January 2014), which includes the Acute Respiratory Infections (ARI) Group's Specialised Register, MEDLINE (1966 to January week 1, 2014), EMBASE (1974 to January 2014) and LILACS (1982 to January 2014). We used the search strategy described in Appendix 1 to search MEDLINE and CENTRAL. The search strategy was adapted to search EMBASE (Appendix 2) and LILACS (Appendix 3). Details of the 2007 update search are in Appendix 4.

Searching other resources

We searched the WHO International Clinical Trials Registry Platform and ClinicalTrials.gov (19 February 2013). We also searched the reference lists of relevant trials, review articles and textbook chapters to identify additional trials, including those published prior to 1966; and we included articles from the authors' personal collections. We also requested unpublished trials from trial authors. In addition, we also contacted drug companies that manufacture antibiotics for the earlier version of this review. There were no language or publication restrictions.

Data collection and analysis

Selection of studies

For the original review (Becker 1997), two authors (LB and JS) independently used the titles and abstracts of the identified citations to exclude trials that clearly did not meet the inclusion criteria of the review. The full paper was obtained for further examination if either review author felt that the trial might possibly meet the criteria. The most common reasons for exclusion were the lack of a control group receiving a placebo, or the inclusion of patients with chronic bronchitis.

Three review authors (LB, JS, TF) reviewed articles, which passed this initial screen by using only the method section of each paper, without reference to the names of the authors, the institution, the journal or the results, to determine their fit with the inclusion criteria for this review. Nine articles passed this second screen but only eight had extractable data. We obtained unpublished data from the other trial (Hueston 1994) from the trial author.

For review updates, two authors screened citations after an updated search was carried out by the Acute Respiratory Infections (ARI) Group for the 2004 update of this review (Fahey 2004). We incorporated two RCTs that met the inclusion criteria into the review. An updated search was carried out by the ARI Group for the 2009 update of the review (Smith 2009). Two review authors (TF, SS) identified and screened three potentially eligible papers and one additional study was included (Little 2005). The ARI

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Group updated the searches for the Smith 2011 update and one additional eligible study was included (Nduba 2008).
For this 2014 updated review, two review authors screened and identified one new eligible study (Little 2013) and one ongoing study (Stocks 2013). One of the ongoing trials has been published and is also included in the review (Llor 2013).

Data extraction and management

More than one review author independently extracted data from original studies for each update of this review. We resolved disagreements by discussion between the review authors.

Assessment of risk of bias in included studies

Three review authors (LB, KJS, TF) evaluated the methodological quality of each trial, while remaining blinded to the names of the trial authors, the institution and the journal in which the trial was published. For previous versions of the review, we assessed the methodological quality of each trial using a scoring system described by Chalmers (Chalmers 1990), which assigned points for randomisation method, blinding of outcome assessment and of patients, intention-to-treat (ITT) analysis, contamination and co-intervention and losses to follow-up. Agreement among the review authors regarding the quality of the articles was high. Disagreements were resolved by discussion and consensus.
For the 2009 update, two review authors (SS, TF) reassessed the original quality of all included studies by using the new 'Risk of bias' guidelines and incorporated this into the 'Risk of bias' tables now presented in this updated review. Two review authors (SS, TF) screened the studies added in the 2011 and 2013 updates.

Measures of treatment effect

The effect measures of choice were risk ratio (RR) for categorical outcomes and mean difference (MD) for continuous data.

Unit of analysis issues

There were no cluster-randomised trials included in this review as it involved a simple drug trial with a placebo comparator. Clinicians were generally blinded to the intervention. We identified no unit of analysis errors.

Dealing with missing data

Where data were missing this was reported within the risk of bias section. We did not adopt any strategies to deal with missing data such as imputation. In general, missing data did not bias the review findings.

Assessment of heterogeneity

Where clinical heterogeneity was considered to be an issue, we undertook a random-effects meta-analysis rather than a fixed-effect meta-analysis. This particularly applied to the most recent analysis added to this updated version of the review (Analysis 6.1).

Assessment of reporting biases

We examined funnel plots for each of the included analyses and none indicated any significant level of reporting bias.

Data synthesis

All previous versions of this review have presented fixed-effect meta-analyses. For this update, we included a range of outcomes under the broad definition of 'clinically improved'. These were clinically heterogeneous so we used a random-effects meta-analysis.

Subgroup analysis and investigation of heterogeneity

We also carried out a subgroup analysis comparing studies using a placebo control or no active treatment.

Sensitivity analysis

We included only studies that limited enrolment to patients with a clinical diagnosis of acute bronchitis or acute productive cough for the primary analysis. We did a sensitivity analysis that included unpublished data from subgroups of patients with a productive cough (Howie 1970) and non-purulent tracheobronchitis (Kaiser 1996) from two studies that enrolled patients with an influenza-like illness or a common cold.

RESULTS

Description of studies

Results of the search

The updated and modified CENTRAL, MEDLINE, EMBASE and LILACS searches in 2014 yielded an additional 799 titles. All of the 17 trials included in the primary analysis enrolled patients with a diagnosis of acute cough or acute lower respiratory tract infection. In one study (Franks 1984), patients were required to produce a sputum sample for analysis as a condition of enrolment.

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Included studies

For this 2014 update, two new studies were added (Little 2013; Llor 2013). These were important additions, particularly the trial by Little 2013 as it is the largest trial conducted to date and included 2061 patients recruited across 12 countries. Patients were randomised to receive amoxicillin or placebo and there was low risk of bias with more than 80% follow-up of participants.

For most studies, clinical findings were used to exclude patients thought to have pneumonia. Four studies included chest radiographs in their protocols - two (Brickfield 1986; Nduba 2008) performed a chest film on all potential participants. In the other two, Scherl 1987 did so on patients with rales or fever and Llor 2013 did so on cases with suspected pneumonia (seven of 416 participants). Both excluded those with radiological evidence of pneumonia or tuberculosis (TB). One study (Stott 1976) excluded patients with any abnormality noted on examination of the chest. Four trials also excluded patients with a clinical syndrome suggesting sinusitis (Dunlay 1987; King 1996; Verheij 1994; Williamson 1984).

In all trials, the duration of illness at entry was less than 30 days. One trial (Stott 1976) limited enrolment to patients ill for less than one week; in five trials the duration was two weeks or less (Brickfield 1986; Evans 2002; Franks 1984; King 1996; Matthys 2000).

Eight of the trials included only adults (Brickfield 1986; Dunlay 1987; Hueston 1994; Little 2013; Llor 2013; Nduba 2008; Verheij 1994; Williamson 1984). The remaining studies included adolescents plus adults (Franks 1984; Scherl 1987; Stott 1976) or patients aged three years (Little 2005) or eight years or older (King 1996).

As for antibiotic treatment, four trials (Scherl 1987; Stott 1976; Verheij 1994; Williamson 1984) used doxycycline, four erythromycin (Brickfield 1986; Dunlay 1987; Hueston 1994; King 1996), one trimethoprim/sulfamethoxazole (Franks 1984), one azithromycin (Evans 2002), one cefuroxime (Matthys 2000), one amoxicillin or erythromycin (Little 2005), two amoxicillin (Little 2013; Nduba 2008) and one co-amoxiclav (Llor 2013).

The majority of studies used a single reassessment visit to evaluate results of the intervention. The timing of this visit varied from study to study, ranging from two to 14 days after the initiation of treatment. Some investigators also asked patients to keep symptom diaries, which were used to determine the duration of symptoms or disability.

Several of the trials provided results of separate analyses of one or more subsets of patients based on characteristics such as cigarette smoking, patient age, duration of symptoms, presence of purulent sputum or illness severity. All patients enrolled in the study by Nduba 2008 were tested for HIV. We have only included results relating to the subgroup of patients who tested negative. The largest study included in the review, which was incorporated in the current update (Little 2013), was adequately powered for a subgroup analysis of patients aged over 60 years.

For the sensitivity analyses, we included unpublished data from two trials. In one (Howie 1970), patients began self-treatment with dimethyl chlortetracycline or placebo if a cold or influenza-like illness was not spontaneously resolving after two days. We included data from a subgroup of patients who had a productive cough prior to beginning treatment. The other study (Kaiser 1996) randomised patients with the common cold to amoxicillin-clavulanic acid or placebo. We included data from a subgroup who had a concomitant diagnosis of non-purulent tracheobronchitis, which incorporates 'acute bronchitis'. Further details on the subgroups of patients included from these studies is provided in the Characteristics of included studies table.

Excluded studies

Studies were excluded for a variety of reasons based on study design and intervention criteria. Full descriptions of such exclusions are detailed in the Characteristics of excluded studies table.

Risk of bias in included studies

Sixteen of the 17 included trials were randomised, double or single-blind evaluations comparing an antibiotic with a placebo. The study added for the 2011 update (Nduba 2008) was the first equivalence RCT included in the review. The earlier study by Little 2005 involved three arms comparing immediate antibiotic therapy, no active treatment or delayed treatment and we included the two arms comparing immediate antibiotic treatment with no treatment only. The study by Llor 2013 added to the current update, involved three arms comparing antibiotic, placebo and anti-inflammatory treatment; we included data from the antibiotic versus placebo arms. Four reports (Brickfield 1986; Howie 1970; Kaiser 1996; Scherl 1987) did not clearly state the randomisation method used. Only one of the articles (Nduba 2008) reported a formal evaluation of the effectiveness of the blinding procedures used. Compliance or adherence with treatment was measured in six studies; in five, there were no differences in the number of pills taken in the antibiotic and placebo groups (Dunlay 1987; Hueston 1994; Little 2013; Nduba 2008; Stott 1976); in the study by King 1996, 94% of the patients who returned for follow-up took at least one-half of their pills and Little 2013 reported > 90% adherence in both groups by day five. Regarding co-interventions with other medications, four trials asked patients to record the use of non-prescription medications and included this as an outcome measure (Dunlay 1987; Franks 1984; Hueston 1994; King 1996); one restricted use to aspirin and acetaminophen, but did not have the patients record this (Scherl 1987); and one reported adjunctive prescriptions, but not use of over-the-counter medications (Verheij 1994). The majority of studies (13 out of 17) followed up more than 80% of participants (details of drop-outs are provided in the Characteristics of included studies table). In some cases, no information about withdrawals was available in the paper or

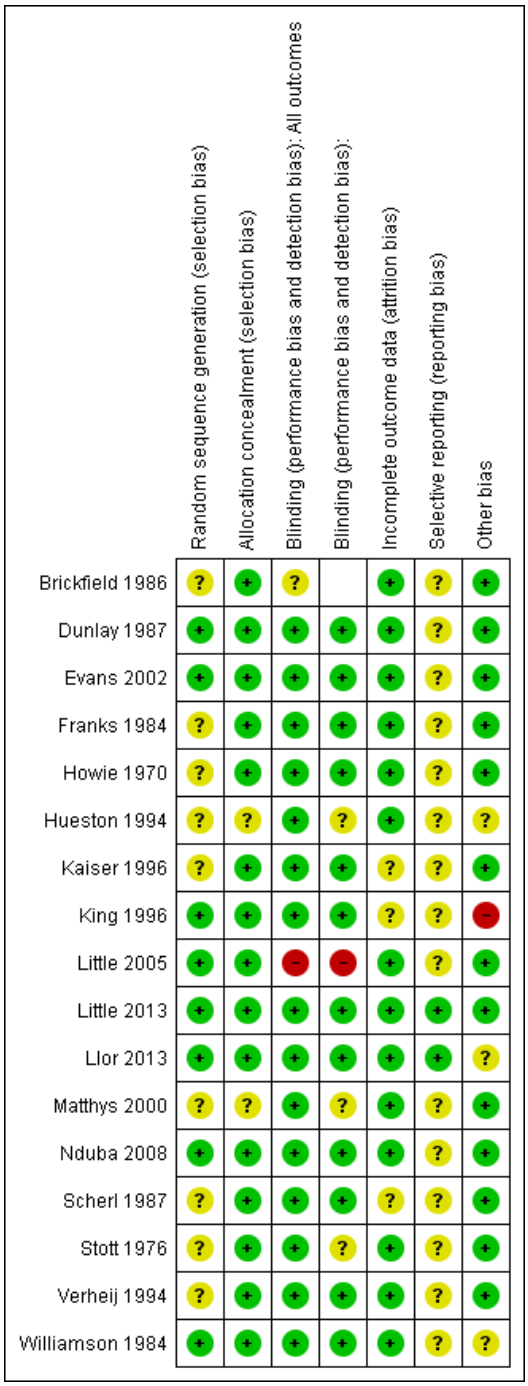
Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

from the authors. However, when information was available, we included outcome data from the last point at which the patients were still in the study. As far as possible, we analyzed patients on an intention-to-treat basis.

The overall risk of bias is presented graphically in Figure 2 and summarised in Figure 3.

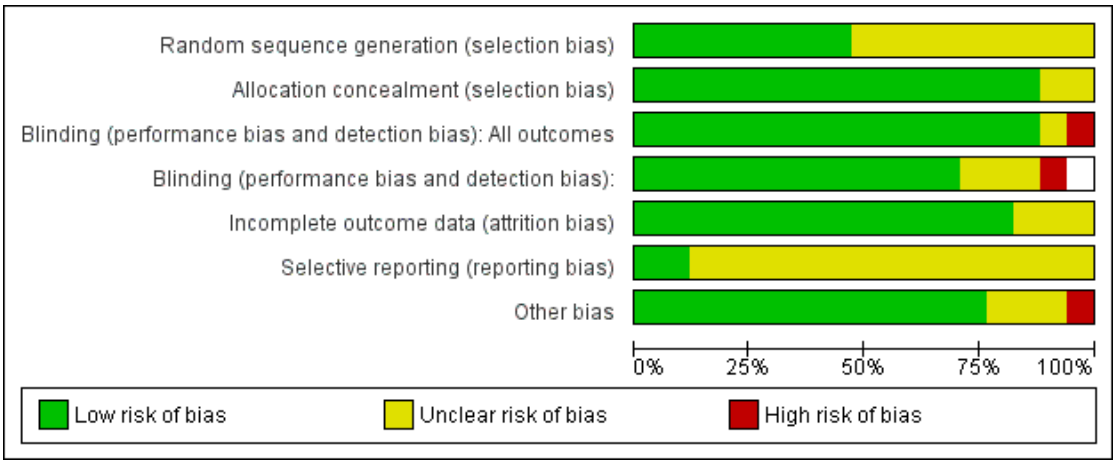
Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Figure 2. 'Risk of bias' summary: review authors' judgements about each methodological quality item for each included study.



Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Figure 3. 'Risk of bias' graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.



Allocation

In general, there was minimal risk of allocation or selection bias; 15 out of 17 studies clearly reported adequate allocation concealment.

Blinding

In general, there was minimal risk of bias relating to lack of blinding with 14 out of 17 studies clearly reporting adequate blinding of outcome assessors.

Incomplete outcome data

The majority of studies had adequate completion of outcome data and there was minimal risk of attrition bias.

Selective reporting

Most trials evaluated several different outcome measures. In some cases, the published reports included detailed data for only those outcomes found to be statistically significant. To minimise this reporting bias, we attempted to obtain additional data from the trial authors; five authors provided this information (Howie 1970; Hueston 1994; Kaiser 1996; King 1996; Williamson 1984). However, we were still unable to include data from Stott 1976 for the outcomes of cough, night cough or activity limitations at follow-up, which were reported in the published trial as being not significantly different between groups.

Other potential sources of bias

The main concern regarding bias was the relatively small numbers of studies that could be included in individual meta-analyses. We have attempted to address this by adding a new broader analysis reflecting clinical improvement. This has been further strengthened by the addition of the largest multi-country trial to date (Little 2013). There were no additional concerns regarding other potential sources of bias.

Effects of interventions

The same outcome measures were not reported in all studies. Some studies reported the presence or absence of various symptoms and signs at a follow-up visit; others reported the mean duration of symptoms; and still others reported only unique symptom scores. Also, in some studies explicit data were available only for outcomes that were significantly different between the antibiotic and placebo groups. Therefore, the number of studies that provide data for the outcomes in this review ranged from three to 11. None of the summary outcomes in the primary analysis exhibited statistically significant heterogeneity apart from the analysis of patient 'clinically improved'. Numbers of studies and participants included in the individual meta-analyses are generally small, though the meta-analysis for 'clinically improved' includes 11 studies and the meta-analysis for adverse events includes 12 studies.

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Primary outcomes

1. Cough-related outcomes

At the follow-up visit, patients given antibiotics were less likely to have a cough (4 studies with 275 participants, risk ratio (RR) 0.64, 95% CI 0.49 to 0.85, NNT 22) (Analysis 1.1; Figure 4) or have a night cough (4 studies with 538 participants, RR 0.67, 95% CI 0.54 to 0.83, NNT 7) (Analysis 2.1). The differences in presence of a productive cough at follow-up and days of productive cough did not reach statistical significance. Antibiotic-treated patients only had a significant reduction in mean duration of cough when the study by Little 2005, which had a no treatment comparison group, was excluded (Figure 5). Llor 2013 also reported no significant difference in the median days of cough between the antibiotic and placebo group. Sensitivity analysis also altered the outcome for the mean duration of productive cough, which was significantly reduced if the Howie 1970 study relating to upper respiratory tract infection was excluded.

Figure 4. Forest plot of comparison: Cough at follow-up visit, outcome: number of patients with cough.

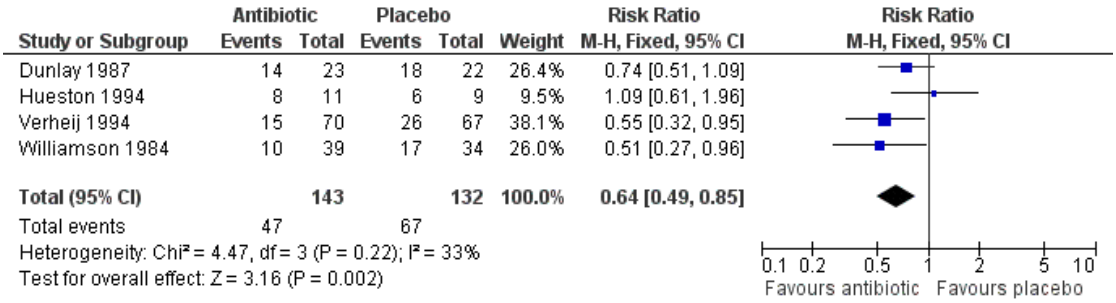
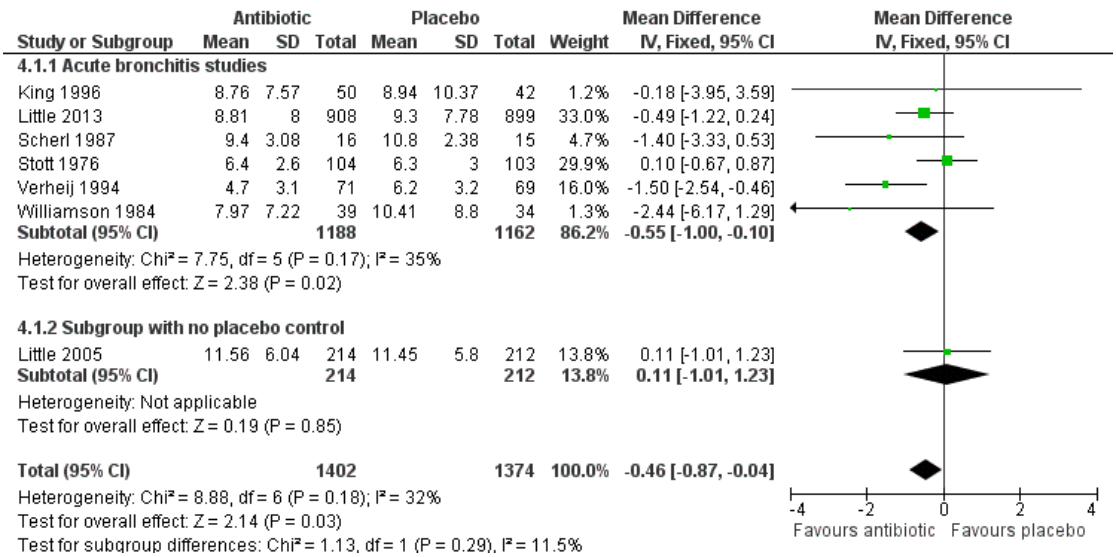


Figure 5. Forest plot of comparison: 8 Days of cough, outcome: mean number of days of cough.



Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

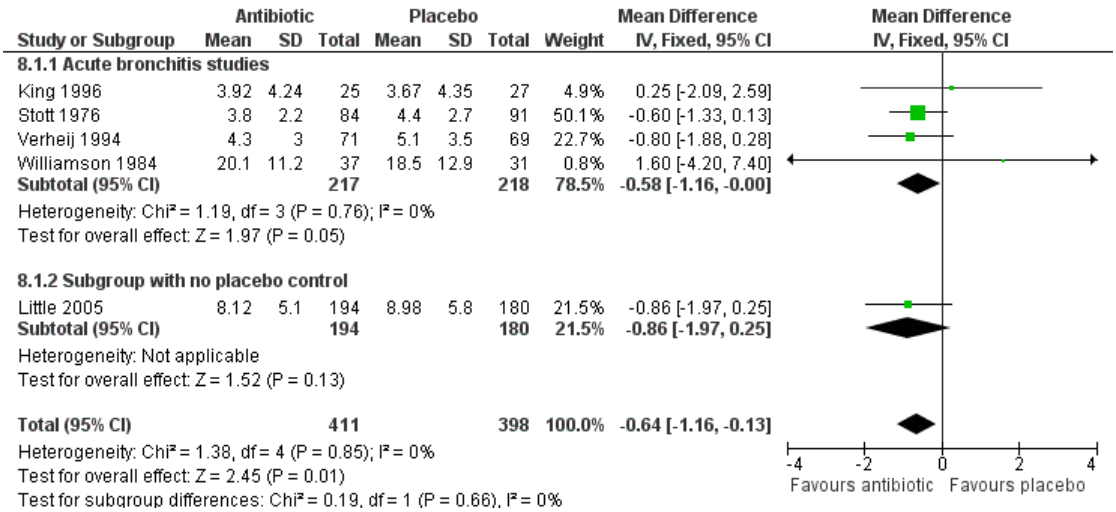
2. Global assessment of improvement by clinicians at follow-up: 'clinically improved'

For the 2011 update of the review, we included an additional analysis that included a broader outcome 'clinically improved', so that as many studies as possible could be included in a meta-analysis. This was particularly important following the inclusion of the Nduba 2008 study in 2011, which was of high quality, included a large number of participants and showed no benefit from antibiotic use. This has been updated and includes additional data from the authors of the largest included study, added to this 2013 update (Little 2013). The data from Little 2013 is based on numbers of patients no longer reporting their symptoms being 'moderately bad' at one week. The published study presents mean symptom severity scores in the first few days, which indicated no significant difference between the intervention and control groups (Little 2013). This outcome reflects the proportions of patients with clinical improvement and incorporates 'cure' as measured by a > 75% reduction in the Acute Bronchitis Severity Score (Nduba 2008), global improvement or being well (Brickfield 1986; Llor 2013; Matthys 2000; Stott 1976; Verheij 1994; Williamson 1984), patient report of no limitations (Dunlay 1987; Evans 2002; Franks 1984) and resolution of symptoms rated as moderately bad, severe or worsening (Little 2013). This analysis includes 11 studies and 3841 participants and shows no statistically significant difference (RR 1.07, 95% CI 0.99 to 1.15, NNT 22) (Analysis 6.1; Figure 1). This is essentially unchanged since the last version of the review although the addition of the data from Little 2013 and Llor 2013 has increased the heterogeneity. A sensitivity analysis removing the studies reporting 'no limitation' made no difference to this result.

3. General clinical outcomes

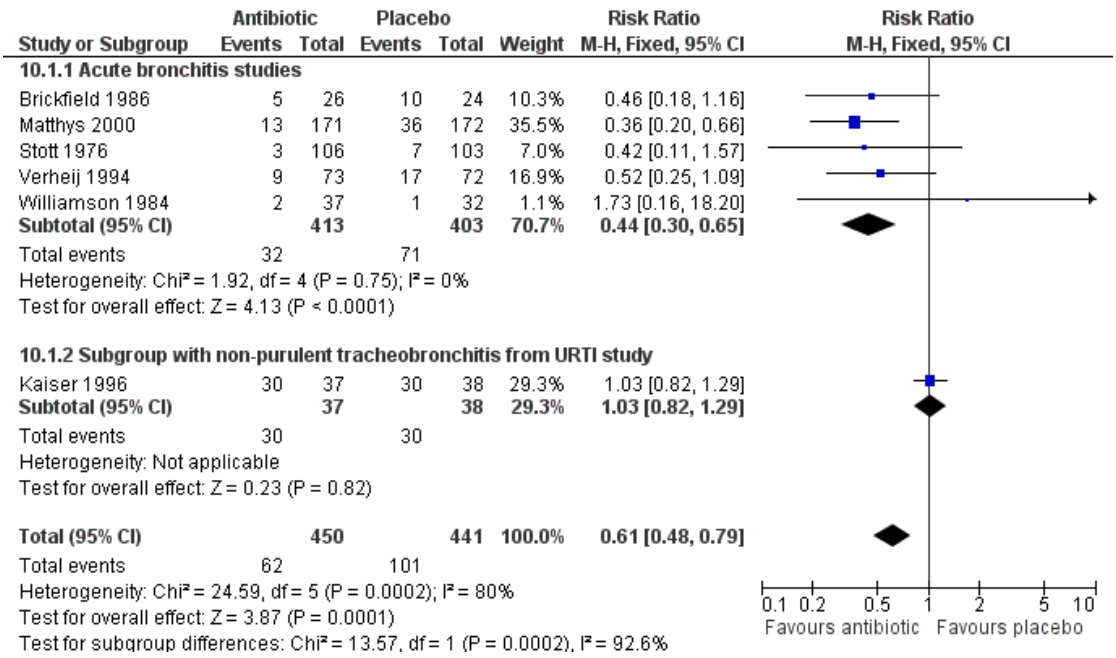
Antibiotic-treated patients also had a reduction in the number of days feeling ill (5 studies with 809 participants, mean difference (MD) -0.64, 95% CI -1.16 to -0.13) (Analysis 8.1; Figure 6) and a reduction in days with impaired activity (6 studies with 767 participants, MD -0.49, 95% CI -0.94 to -0.04) (Analysis 9.1). There was no significant difference in proportions of patients with activity limitations at follow-up. Patients on antibiotics were more likely to be unimproved by the clinician's global assessment (6 studies with 891 participants, RR 0.61, 95% CI 0.48 to 0.79, NNT 25) (Analysis 10.1; Figure 7) and have an abnormal lung exam (5 studies with 613 participants, RR 0.54, 95% CI 0.41 to 0.70, NNT 6) (Analysis 11.1). Additional clinical outcomes were reported by Little 2013 who found no significant difference in mean symptom severity scores on days two to four (intervention score 1.62 (standard deviation (SD) 0.84) versus control score 1.69 (SD 0.84), P = 0.07) and Evans 2002 found that azithromycin had no benefit in terms of health-related quality of life at day three and day seven follow-up. Llor 2013 also reported no difference in time to overall symptom resolution between groups.

Figure 6. Forest plot of comparison: Days of feeling ill, outcome: mean number of days of feeling ill.



Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Figure 7. Forest plot of comparison: Not improved by physician's global assessment at follow-up visit, outcome: number of patients not improved.



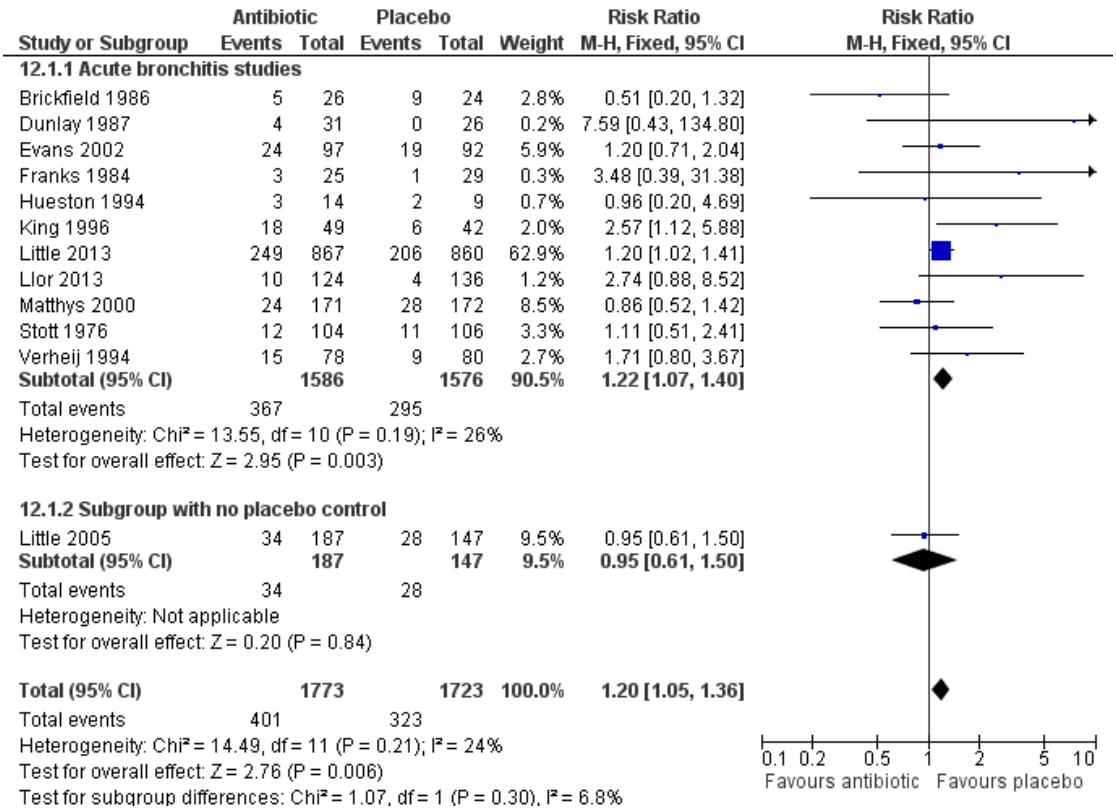
Secondary outcomes

1. Adverse effects

With four exceptions (Brickfield 1986; Little 2005; Matthys 2000; Nduba 2008), all of the studies found that patients in the antibiotic group reported more adverse effects than did patients receiving a placebo (Figure 8). The RR of adverse effects in the antibiotic-treated group was statistically significant at 1.20 (12 studies with 3496 participants, 95% CI 1.05 to 1.36, NNT 5) (Analysis 12.1). The most commonly reported side effects involved gastrointestinal symptoms such as nausea, vomiting or diarrhea. Headaches, skin rash and vaginitis also occurred. Side effects seemed mild as only 0% to 13% (overall 3.7%) of volunteers withdrew for this reason and no deaths were reported.

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Figure 8. Forest plot of comparison: Number of patients with adverse effects.



Subgroups

We were not able to obtain enough explicit data from the studies for various patient subgroups, therefore we did not carry out any sensitivity analyses based on patient characteristics (such as age, duration of illness or smoking status). Little 2013 was adequately powered to assess the effect in the subgroup of patients aged over 60 and found no significant benefit in this group. The results in the individual studies for subgroup analyses were mixed. In one trial, all of the significantly improved outcomes from antibiotics occurred in non-smokers (Brickfield 1986). The other seven trials reported that they found no differences in antibiotic effectiveness for smokers versus non-smokers but included no data on these comparisons in their published reports. Verheij 1994, using multiple regression, found that two subsets of patients were more likely to improve with doxycycline than placebo: patients over 55 years and patients with very frequent cough who felt ill. Scherl 1987 found that only patients without coryza or sore throat had fewer days of cough or sputum with doxycycline. The only study to use Gram stains (Franks 1984) reported an earlier return to work for patients with a positive Gram stain who were treated with antibiotics. Nduba 2008 also examined whether use of amoxicillin was more effective than placebo in patients who had tested positive for HIV and found no difference, though all patients had received a chest X-ray and those with any abnormal signs were excluded. Little 2005 was added to the 2009 update and found no significant difference in outcomes between groups treated with immediate antibiotics compared with no antibiotic treatment. As this study did not involve a placebo control we included it in the analyses, where appropriate data were available, as a subgroup to highlight this difference. The one study included in the 2011 update (Nduba 2008) was powered to detect equivalence between antibiotic and placebo and found no significant difference. In fact, the point estimates favoured placebo treatment (84% cured on placebo versus 82.4%% cured on amoxicillin). The largest included study, which was added in the 2013 update, was included in the meta-analyses of 'clinically improved' and adverse effects (Little 2013).

DISCUSSION

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Summary of main results

There are mixed results across studies with some suggesting marginal benefits for antibiotics, though these are of doubtful clinical significance. However, the inclusion of the largest multi-centre study of the effectiveness of antibiotics in patients with lower respiratory tract infections strengthens the evidence and also highlights a statistically significant increase in adverse events in the antibiotic-treated groups. However, it is possible that older patients with multimorbidities may not have been recruited to trials so the evidence guiding decision making in this group of patients is less certain.

Overall completeness and applicability of evidence

In general, the available evidence suggests we should not be using antibiotics to treat acute bronchitis or lower respiratory tract infections when pneumonia is not expected. There is a modest benefit from antibiotics for some outcomes but these are of minimal clinical significance. Any benefit is even less apparent in the sensitivity analysis, which included data from subgroups of patients with productive cough of short duration (two to four days) in conjunction with the common cold. Of the two trials in the primary analysis that limited enrolment to patients who had been ill for less than one week, one did not show any benefit from antibiotics (Stott 1976), whilst the other showed modest benefit with antibiotic (Matthys 2000).

It is possible that the overall benefit noted from antibiotics resulted from the inclusion in some trials of patients who may have had pneumonia instead of acute bronchitis. There was variation between studies on whether chest X-rays were conducted as part of evaluations. Only one trial (Brickfield 1986) obtained chest radiographs on all patients and then excluded those whose films were consistent with pneumonia. In Little 2013, a positive chest X-ray was not an automatic exclusion criteria though some patients dropped out following such a finding and further publications on this are planned (author communication). All other studies either excluded or obtained chest radiographs in patients with clinical findings of suspected pneumonia (which in most studies were focal findings on chest examination). Individual signs (such as crackles or fever) are not sensitive (Metlay 1997a), therefore their absence cannot be relied on to rule out pneumonia. On the other hand, since the prevalence of pneumonia in outpatients who present with cough is generally low (less than 5% in the USA) (Metlay 1997b), it is unlikely that a significant number of patients in these trials had pneumonia. Further evidence for this is that only three patients who were randomised to placebo among all nine primary trials were subsequently diagnosed with pneumonia (two patients in Stott 1976 and one in Scherl 1987). In addition, this review is designed to test the effectiveness of treatment for acute bronchitis in clinical practice and it is not standard practice to confirm the diagnosis of acute bronchitis with a chest X-ray unless there is a clinical suspicion of underlying pneumonia. If we had only included studies with chest X-ray confirmation of diagnosis it would have limited the generalisability of the review findings.

Quality of the evidence

Since there is no gold standard test, the diagnosis of acute bronchitis must be made on clinical grounds. All of the trials excluded patients with chronic pulmonary disease and enrolled patients with recent onset of a respiratory illness with a productive cough. The results of the studies in the primary analysis that included patients with a productive cough, without specifically stating that the patients had acute bronchitis, were similar to the studies that used this specific terminology, as one showed some benefits from antibiotics (Verheij 1994) and one did not (Stott 1976). Clinical characteristics of patients did vary somewhat among studies regarding the duration of illness and associated symptoms and physical findings but were consistent with definitions generally used by primary care physicians (Oeffinger 1997; Verheij 1990). Therefore, these results would appear to be generalisable to the management of acute bronchitis in community practices.

Potential biases in the review process

This review may also be subject to bias because although we have now included 16 trials and 3656 participants, it is possible that some patient subgroups are under-represented as they may not have been recruited into the original trials. Little 2013 points out that while they included a large sample of older patients, more severely ill older people with multimorbidities were unlikely to have been approached to participate in the trial and in these types of patients, their results should be interpreted with caution and this applies to the review results also.

Agreements and disagreements with other studies or reviews

In the current update of the review, we have included a large multi-country trial that shows no benefits from antibiotics even in older patients. Further analyses of the data from this study are ongoing as part of Workpackage 10 of the GRACE program (http://www.grace-lrti.org). It should be noted that a recent large observational study examining symptom resolution in 2714 patients with acute cough who had been prescribed amoxicillin across 13 European countries found that symptom resolution was quicker in those receiving no antibiotic (Butler 2010).

AUTHORS' CONCLUSIONS

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Implications for practice

This review confirms the impression of clinicians that antibiotics have limited, if any, beneficial effects in acute bronchitis. Where there appear to be some benefits, they are slight (such as the small improvement in mean duration of cough of less than one day) and may be of questionable clinical significance. The most recently published placebo-controlled randomised controlled trial (RCT) confirms these findings and was carried out in 12 countries, improving the generalisability of the review findings (Little 2013). The RCT included in the last update of the review in 2011 also showed no difference in cure rates between those prescribed amoxicillin and those given placebo (Nduba 2008). This trial was particularly important as it was set in a low-income country and may increase the generalisability of the review. However, the inclusion of a range of trials in different settings does also increase heterogeneity.

While this review suggests limited if any benefit from antibiotics, one could argue for prescribing antibiotics for acute bronchitis because studies of patient utilities for antibiotic treatment for respiratory infections suggest that even small benefits are seen as important by some patients (Herman 1984) and because the adverse effects associated with antibiotic treatment are minor and disappear when the medication is discontinued. On the other hand, arguments against prescribing antibiotics can be made because the modest benefits from antibiotics may not outweigh their costs, adverse effects or negative consequences on antibiotic resistance patterns and patient expectations. Also, as noted above, the current update provides clearer evidence on the lack of effectiveness of antibiotics for acute bronchitis.

It is likely that, as with other respiratory infections (Dagnelie 1996; Kaiser 1996), antibiotics may be only effective for a subset of patients with acute bronchitis. It seems that patients who have other typical symptoms of an upper respiratory tract infection and who have been ill for less than one week may be the least likely to benefit from antibiotics. A large recent cohort study within the UK General Practice Research Database has indicated that the risk of pneumonia as a complication of lower respiratory tract infection was substantially reduced in elderly patients when antibiotics had been prescribed immediately (Petersen 2007). However, a likely confounding factor in this study was the fact that sicker patients and those more likely to suffer complications were offered immediate antibiotics, introducing potential bias (Coenen 2007). The trials that have been performed to date do not offer a clear way to differentiate patients with acute bronchitis who might benefit from antibiotic therapy from those who might not. In light of this uncertainty, it is especially important for clinicians to share the decision about whether to use antibiotics or not with their patients, using the expected outcomes and their magnitude from this review as a basis for their discussion.

In terms of interventions designed to reduce unnecessary antibiotic prescribing, some organisational and educational strategies have been shown to be helpful. Use of delayed or deferred antibiotic when patients consult with symptoms of acute bronchitis is of some value (Dowell 2001). In a randomised trial in 22 UK practices, 191 patients were randomised to either immediate or delayed antibiotic (prescription lodged at the family practice reception and patients were invited to collect it after one week, if required). Over half (55%) in the delayed arm did not pick up their prescriptions, though compared to the immediate arm patients, they were less satisfied with this strategy (Dowell 2001). In a randomised trial of a patient information leaflet in 212 patients with acute bronchitis for whom antibiotics were judged to be unnecessary by their family doctor, the leaflet reduced uptake compared to those without any information (49% versus 63%, risk ratio 0.76) (Macfarlane 2002). This review contains a subgroup from a more recent UK trial which tested the effectiveness of three prescribing strategies and an information leaflet for acute lower respiratory tract infections (Little 2005). The authors concluded that no offer or a delayed offer of antibiotics for acute uncomplicated lower respiratory tract infection is acceptable and is associated with little difference in symptom resolution. The authors argue that the strategy of delayed or no prescribing is very likely to reduce antibiotic use and beliefs in the effectiveness of antibiotics for this condition. A recent review concluded that complex interventions that included education for physicians were most likely to be effective in optimising antibiotic prescribing in primary care settings (van der Velden 2012).

Implications for research

There is a widespread belief among clinicians and patients that antibiotics provide effective treatment for acute bronchitis. There is also widespread opinion among experts that antibiotic therapy is unwarranted in this condition. The results of this review indicate that there are, at most, limited benefits for some patients and this must be placed in the context of the significant increase in adverse events in the antibiotic group. However, it is also possible that any apparent benefits from antibiotics are overestimated.

Ongoing research efforts should also be directed at the identification of subsets of patients who are most likely or least likely to benefit from antibiotic treatment (Coenen 2007; Little 2013). Patient age, duration and severity of illness, chest examination findings, sputum Gram stains, C-reactive protein levels (Jonsson 1997) and cigarette smoking are variables which may be important in differentiation of these patient subsets. The ongoing GRACE programme (genomics to combat resistance against antibiotics in community-acquired lower respiratory tract infections in Europe, http://www.grace-lrti.org) may provide answers to some of these questions (Coenen 2007). Given the controversy around the term 'acute bronchitis' it will also be important for researchers to be very clear on their inclusion criteria to allow comparison across studies. Finally, given the small impact, at best, of antibiotics on

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

patient symptoms, investigators should continue the search for other effective means of relieving the most troublesome symptoms for patients suffering from acute bronchitis.

ACKNOWLEDGEMENTS

We wish to thank Sarah Thorning from the ARI Group for assistance with the updated search in 2009, 2011 and 2013; William Grant for statistical assistance on the original review; the investigators of the studies included in this review, especially William Hueston, Dana King, Harold Williamson, John Howie and Laurent Kaiser who provided us with unpublished data; and Mike Stephenson and Amy Schende who also provided unpublished information. We would like to acknowledge the work of Dr Rick Glazier who conceived and designed the original review; graded and extracted data from trials; interpreted data independently, and then as a group, and co-wrote the 2004 update. We would also like to acknowledge Dr Warren McIsaac who conceived and designed the original review and co-wrote the first update. We wish to thank the following people for commenting on the 2009 updated review: Fiona Clay, Jane Nadel, Theo Verheij, Rob Ware and Peter Morris. We wish to thank Peter Morris, Sree Nair, Theo Verheij, Amanda Young and Teenah Handiside for comments and suggestions regarding the 2011 update. We thank Beth Stuart and Paul Little who provided additional data for this 2013 update. Finally, we wish to thank Raghda Rashad, Theo Verheij, Conor Teljeur, and Peter Morris for commenting on this 2013 update.

REFERENCES

References to studies included in this review

Brickfield 1986 *{published data only}*
Brickfield FX, Carter WH, Johnson RE. Erythromycin in the treatment of acute bronchitis in a community practice. *Journal of Family Practice* 1986;**23**:119–22.

Dunlay 1987 *{published data only}*
Dunlay J, Reinhardt R, Roi LD. A placebo-controlled, double-blind trial of erythromycin in adults with acute bronchitis. *Journal of Family Practice* 1987;**25**:137–41.

Evans 2002 *{published data only}*
Evans AT, Husain S, Durairaj L, Sadowski LS, Charles-Damte M, Wang Y. Azithromycin for acute bronchitis: a randomised, double-blind, controlled trial. *Lancet* 2002; **359**:1648–54.

Franks 1984 *{published data only}*
Franks P, Gleiner JA. The treatment of acute bronchitis with trimethoprim and sulfamethoxazole. *Journal of Family Practice* 1984;**19**:185–90.

Howie 1970 *{published and unpublished data}*
Howie JGR, Clark GA. Double-blind trial of early demethychlortetracycline in minor respiratory illness in general practice. *Lancet* 1970;**28**(2 (7683)):1099–102.

Hueston 1994 *{published and unpublished data}*
Hueston WJ. Albuterol delivered by metered-dose inhaler to treat acute bronchitis. *Journal of Family Practice* 1994;**39** (5):437–40.

Kaiser 1996 *{published and unpublished data}*
Kaiser L, Lew D, Hirschel B, Auckenthaler R, Morabia A, Heald A, et al.Effects of antibiotic treatment in the subset of common-cold patients who have bacteria in nasopharyngeal secretions. *Lancet* 1996;**347**:1507–10.

King 1996 *{published and unpublished data}*
King DE, Williams WC, Bishop L, Shechter A. Effectiveness of erythromycin in the treatment of acute bronchitis. *Journal of Family Practice* 1996;**42**:601–5.

Little 2005 *{published and unpublished data}*
Little P, Rumsby K, Kelly J, Watson L, Moore M, Warner G, et al.Information leaflet and antibiotic prescribing strategies for acute lower respiratory tract infection. *JAMA* 2005;**293** (24):3029–35.

Little 2013 *{published and unpublished data}*
Little P, Stuart B, Moore M, Coenen S, Butler CB, Godyscki-Cwirko M, et al.Amoxicillin for acute lower-respiratory-tract infection when pneumonia is not suspected: a 12 country, randomised, placebo-controlled trial. *Lancet Infectious Diseaes* 2013;**13**:123–9.

Llor 2013 *{published data only}*
Llor C, Moragas A, Bayona C, Morros R, Pera H, Cots JM, et al.Efficacy of anti-inflammatory or antibiotic treatment in patients with non-complicated acute bronchitis and discoloured sputum: randomised controlled trial. *BMJ* 2013;**347**:f5762.

Matthys 2000 *{published data only}*
Matthys H, de Mey C, Carls C, Rys A, Geib A, Wittig T. Efficacy and tolerability of myrtol standardised in acute bronchitis. *Arzmeimittel Forschung* 2000;**50**:700–11.

Nduba 2008 *{published data only}*
Nduba VN, Mwachari CW, Magaret AS, Park DR, Kigo A, Hooton TM, et al.Placebo found equivalent to amoxicillin for treatment of acute bronchitis in Nairobi, Kenya: a triple blind, randomised equivalence study. *Thorax* 2008;**63**: 999–1005.

Scherl 1987 *{published data only}*
Scherl ER, Riegler SL, Cooper JK. Doxycycline in acute bronchitis: a randomized double-blind trial. *Journal of the Kentucky Medical Association* 1987;**85**:539–41.

Stott 1976 *{published data only}*
Stott NCH, West RW. Randomised controlled trial of antibiotics in patients with cough and purulent sputum. *British Medical Journal* 1976;**2**:556–9.

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Verheij 1994 *{published data only}*
Verheij TJM, Hermans J, Mulder JD. Effects of doxycycline in patients with acute cough and purulent sputum: a double blind placebo controlled trial. *British Journal of General Practice* 1994;**44**:400–4.

Williamson 1984 *{published and unpublished data}*
Williamson HA. A randomized controlled trial of doxycycline in the treatment of acute bronchitis. *Journal of Family Practice* 1984;**19**:481–6.

References to studies excluded from this review

Bateiha 2002 *{published data only}*
Batieha A, Yahia G, Mahafzeh T, Omari M, Momani A, Dabbas M. No advantage of treating acute respiratory tract infections with azithromycin in a placebo-controlled trial. *Scandinavian Journal of Infectious Diseases* 2002;**34**(4): 243–7.

Christ-Crain 2004 *{published data only}*
Christ-Crain M, Jaccard-Stolz D, Bingisser R, Gencay MM, Huber PR, Tamm M, et al.Effect of procalcitonin-guided treatment on antibiotic use and outcome in lower respiratory tract infections: cluster-randomised, single-blinded intervention trial. *Lancet* 2004;**363**(9409):600–7.

Dowell 2001 *{published data only}*
Dowell J, Pitkethly M, Bain J, Martin S. A randomised controlled trial of delayed antibiotic prescribing as a strategy for managing uncomplicated respiratory tract infection in primary care. *British Journal of General Practice* 2001;**51**: 200–5.

Gordon 1974 *{published data only}*
Gordon M, Lovell S, Dugdale AE. The value of antibiotics in minor respiratory illness in children: a controlled trial. *Medical Journal of Australia* 1974;**1**:304–6.

Gottfarb 1994 *{published data only}*
Gottfarb P, Brauner A. Children with persistent cough - outcome with treatment and role of Moraxella catarrhalis. *Scandinavian Journal of Infectious Diseases* 1994;**26**:545–51.

Stephenson 1989 *{unpublished data only}*
Stephenson MJ. Antibiotics for acute bronchitis: a randomised controlled trial. Unpublished data 1989.

Thomas 1978 *{published data only}*
Thomas S. Antibiotics for cough and purulent sputum. British Medical Journal 1978; Vol. 2, issue 11:1374.

Additional references

Ayres 1986
Ayres JG. Seasonal pattern of acute bronchitis in general practice in the United Kingdom 1976-83. *Thorax* 1986;**41**: 106–10.

Boldy 1990
Boldy DAR, Skidmore SJ, Ayres JG. Acute bronchitis in the community: clinical features, infective factors, changes in pulmonary function and bronchial reactivity to histamine. *Respiratory Medicine* 1990;**84**:377–85.

Butler 2010
Butler CC, Hood K, Kelly MJ, Goossens H, Verheij T, Little P, et al.Treatment of acute cough/lower respiratory tract infection by antibiotic class and associated outcomes: a 13 European country observational study in primary care. *Journal of Antimicrobial Chemotherapy* 2010;**65**(11): 2472–8.

CDC 2013
Centre For Disease Control and Prevention. Overview of bronchitis. http://www.cdc.gov/getsmart/antibiotic-use/uri/bronchitis.html 2013 (accessed 11 November 2013).

Chalmers 1990
Chalmers I, Adams M, Dickersin K, Hetherington J, Tarnow-Mordi W, Meinert C, et al.A cohort study of summary reports of controlled trials. *JAMA* 1990;**263**: 1401–5.

Coenen 2007
Coenen S, Goossens H. Antibiotics for respiratory tract infections in primary care. *BMJ* 2007;**335**:946–7.

Dagnelie 1996
Dagnelie CF, Van Der Graf Y, DeMelker RA. Do patients with sore throat benefit from penicillin? A randomized double-blind placebo-controlled clinical trial with penicillin V in general practice. *British Journal of General Practice* 1996;**46**:589–93.

Delozier 1989
Delozier JE, Gagnon RO. National Ambulatory Care Survey 1989 Summary. Advanced Data No. 203. *National Center for Health Statistics* 1989;**203**:1–11.

ECDC 2013
European Centre for Disease Control. Trend of antimicrobial consumption by country. http://www.ecdc.europa.eu/en/healthtopics/antimicrobial˙resistance/esac-net-database/Pages/trend-consumption-by-country.aspx 2013 (accessed 8 November 2013).

Falck 1994
Falck G, Heyman L, Gnarpe J, Gnarpe H. Chlamydia pneumoniae (TWAR): a common agent in acute bronchitis. *Scandinavian Journal of Infectious Diseases* 1994;**26**:179–87.

Foy 1993
Foy HM. Infections caused by Mycoplasma pneumoniae and possible carrier state in different populations of patients. *Clinical Infectious Diseases* 1993;**17**(Suppl 1):37–46.

Gonzales 1995
Gonzales R, Sande M. What will it take to stop physicians from prescribing antibiotics in acute bronchitis?. *Lancet* 1995;**345**:665.

Gonzales 1997
Gonzales R, Steiner JF, Sande MA. Antibiotic prescribing for adults with colds, upper respiratory tract infections, and bronchitis by ambulatory care physicians. *JAMA* 1997;**278**: 901–4.

Grayston 1993
Grayston JT, Aldous MB, Easton A, Wang SP, Kuo CC, Campbell LA, et al.Evidence that Chlamydia pneumoniae

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

causes pneumonia and bronchitis. *Journal of Infectious Diseases* 1993;**168**:1231–5.

Gulliford 2011
Gulliford MC, van Staa T, McDermott L, Dregan A, McCann G, Ashworth M, et al.Cluster randomised trial in the General Practice Research Database: 1. Electronic decision support to reduce antibiotic prescribing in primary care (eCRT study). *Trials* 2001;**12**:115.

Henry 1995
Henry D, Ruoff GE, Rhudy J, Puopolo A, Drehobl M, Schoenberger J, et al.Effectiveness of short-course therapy (5 days) with cefuroxime axetil in treatment of secondary bacterial infections of acute bronchitis. *Antimicrobial Agents and Chemotherapeutics* 1995;**39**:2528–34.

Herman 1984
Herman JM. Patients' willingness to take risks in the management of pharyngitis. *Journal of Family Practice* 1984; **6**:767–72.

Herwaldt 1991
Herwaldt LA. Pertussis in adults: what physicians need to know. *Archives of Internal Medicine* 1991;**151**:1510–2.

Hueston 1997
Hueston WJ. Antibiotics: neither cost effective nor 'cough' effective. *Journal of Family Practice* 1997;**44**:261–5.

Jonsson 1997
Jonsson JS, Sigurdsson JA, Kristinsson KG, Guonadottir M, Magnusson S. Acute bronchitis in adults: how close do we come to its aetiology in general practice?. *Scandinavian Journal of Primary Health Care* 1997;**15**:156–60.

Laurenzi 1961
Laurenzi GA, Potter RT, Kass EH. Bacteriologic flora of the lower respiratory tract. *New England Journal of Medicine* 1961;**265**:1273–8.

Lefebvre 2011
Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins JPT, Green S editor(s). *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration. Available from www.cochrane-handbook.org*. Chichester, UK: Wiley-Blackwell, 2011.

Macfarlane 1993
Macfarlane JR, Colville A, Guion A, Macfarlane RM, Rose DH. Prospective study of aetiology and outcome of adult lower-respiratory tract infections in the community. *Lancet* 1993;**341**:511–4.

Macfarlane 1994
Macfarlane JT, Prewett J, Guion A, Gard P. Community acquired lower respiratory infection: bacterial infection not uncommon (letter). *BMJ* 1994;**308**:1239.

Macfarlane 2001
Macfarlane J, Holmes W, Gard P, Macfarlane R, Rose D, Weston V, et al.Prospective study of the incidence, aetiology and outcome of adult lower respiratory tract illness in the community. *BMJ* 2001;**56**:109–14.

Macfarlane 2002
Macfarlane J, Holmes W, Gard P, Thornhill D, Macfarlane R, Hubbard R. Reducing antibiotic use for acute bronchitis in primary care: blinded, randomised controlled trial of patient information leaflet. *BMJ* 2002;**324**:91–4.

Mainous 1996
Mainous AG, Zoorob RJ, Hueston WJ. Current management of acute bronchitis in ambulatory care. *Archives of Family Medicine* 1996;**5**:79–83.

Metlay 1997a
Metlay JP, Kapoor WN, Fine MJ. Does this patient have community-acquired pneumonia? Diagnosing pneumonia by history and physical examination. *JAMA* 1997;**278**: 1440–5.

Metlay 1997b
Metlay JP, Stafford RS, Singer DE. National trends in the use of antibiotics by primary care physicians for adult patients with cough. *Archives of Internal Medicine* 1998; **158**:1813–8.

Meza 1994
Meza RA, Bridges-Webb C, Sayer GP, Miles DA, Traynor V, Neary S. The management of acute bronchitis in general practice: results from the Australian morbidity and treatment survey, 1990-1991. *Australian Family Physician* 1994;**23**(8):1550–3.

Molstad 1992
Molstad S, Arvidsson E, Eliasson I, Hovelius B, Kamme C, Schalén C. Production of beta-lactamase in respiratory tract bacteria in children: relationship to antibiotic use. *Scandinavian Journal of Primary Health Care* 1992;**10**: 16–20.

Oeffinger 1997
Oeffinger KC, Snell LM, Foster BM, Panico KG, Archer RK. Diagnosis of acute bronchitis in adults: a national survey of family physicians. *Journal of Family Practice* 1997; **45**:402–9.

Petersen 2007
Petersen I, Johnson AM, Islam A, Duckworth G, Livermore DM, Hayward AC. Protective effect of antibiotics against serious complications of common respiratory tract infections: retrospective cohort study with the UK General Practice Research Database. *BMJ* 2007;**335**:982. [DOI: 10.1136/bmj.39345.405243.BE]

Robertson 1987
Robertson PW, Goldberg H, Jarvie BH, Smith DD, Whybin LR. Bordetella pertussis infection: a cause of persistent cough in adults. *Medical Journal of Australia* 1987;**146**:522–5.

Smith 1986
Smith JMB, Lockwood BM. Commensal or pathogen? The growing dilemma facing the general practitioner. *New Zealand Medical Journal* 1986;**99**:242–3.

Straand 1997
Straand J, Skinio Rokstad K, Sandvik H. Prescribing systemic antibiotics in general practice: a report from

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

the More and Romsdal Prescription Study. *Scandinavian Journal of Primary Health Care* 1998;**16**:121–7.

Stuart-Harris 1965
Stuart-Harris CH, Andrewes C, Andrews BE, Beale AJ, Gardner PS, Grist NR, et al.A collaborative study of the aetiology of acute respiratory infections in Britain 1961-4. *British Medical Journal* 1965;**29**:319–26.

Thom 1994
Thom DH, Grayston JE, Campbell LA, Kuo CC, Diwan VK, Wang SP. Respiratory infection with Chlamydia pneumoniae in middle-aged and older adult outpatients. *European Journal of Clinical Microbiology and Infectious Diseases* 1994;**13**:785–92.

van der Velden 2012
van der Velden A, Pijpers EJ, Kuyvenhoven M, Tonkin-Crine SKG, Little P, Verheij TJM. Effectiveness of physician-targeted interventions to improve antibiotic use for respiratory tract infections. *British Journal of General Practice* 2012;**62**(605):e801–7.

Verheij 1990
Verheij TJM, Hermans J, Kaptein AA, Mulder JD. Acute bronchitis: general practitioners' views regarding diagnosis and treatment. *Family Practice* 1990;**7**:175–80.

References to other published versions of this review

Becker 1997
Becker L, Glazier R, McIsaac W, Smucny J. Antibiotics for acute bronchitis. *Cochrane Database of Systematic Reviews* 1997, Issue 4. [DOI: 10.1002/14651858.CD000245.pub2]

Fahey 1998
Fahey T, Stocks N, Thomas T. Quantitative systematic review of randomised controlled trials comparing antibiotic with placebo for acute cough in adults. *BMJ* 1998;**316**: 906–10.

Fahey 2004
Fahey T, Smucny J, Becker L, Glazier R. Antibiotics for acute bronchitis. *Cochrane Database of Systematic Reviews* 2004, Issue 4. [DOI: 10.1002/14651858.CD000245.pub2]

Smith 2009
Smith SM, Fahey T, Smucny J, Becker LA. Antibiotics for acute bronchitis. *Cochrane Database of Systematic Reviews* 2009, Issue 1. [DOI: 10.1002/14651858.CD000245.pub2]

Smith 2011
Smith SM, Fahey T, Smucny J, Becker LA. Antibiotics for acute bronchitis. *Cochrane Database of Systematic Reviews* 2011, Issue 11. [DOI: 10.1002/14651858.CD000245.pub2]

Smucny 1998
Smucny JJ, Becker LA, Glazier RH, McIsaac W. Are antibiotics effective treatment for acute bronchitis? A meta-analysis. *Journal of Family Practice* 1998;**47**:453–60.

Smucny 2000
Smucny J, Fahey T, Becker L, Glazier R, McIsaac W. Antibiotics for acute bronchitis. *Cochrane Database of Systematic Reviews* 2000, Issue 4. [DOI: 10.1002/14651858.CD000245.pub2]

* *Indicates the major publication for the study*

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Brickfield 1986

Methods	Double-blinded RCT
Participants	52 adults (aged 18 to 65), with 2 weeks or less of lower respiratory infection with sputum production and no evidence of pneumonia clinically or radiographically. Drop-outs = 2/52
Interventions	Enteric-coated erythromycin 333 mg TID for 7 days versus placebo. Volunteers kept daily logs of multiple symptoms and were re-examined on day 8
Outcomes	Cough, sputum, fever, rhinorrhoea, chest discomfort, earache, sore throat, work disability, feeling ill and nausea daily; and clinical impression at follow-up
Notes	29 volunteers had sputum cultured (27 = normal flora, 1 = *H. influenza*, 1 = *S. pneumonia*) , outcomes not reported; 17/23 had more than 5 white blood cells (wbc) on Gram stain. Fewer than 30% of eligible patients opted to volunteer (most wanted antibiotics)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Unclear risk	Not reported
Other bias	Low risk	

Dunlay 1987

Methods	Double-blinded RCT
Participants	63 adults (age 18 or older) with productive cough (mean duration = 7 days) and no clinical evidence of sinusitis or pneumonia. Drop-outs = 15 (6 - no follow-up at all; 9 - stopped taking pills during trial, authors state that no difference in results with or

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Dunlay 1987 (*Continued*)

	without the partial data from the latter 9)
Interventions	Enteric-coated erythromycin base, 333 mg TID for 10 days, versus placebo. Volunteers kept daily logs of 5 symptoms and had follow-up visit at approximately day 14
Outcomes	Day cough, night cough, sputum production, congestion, sore throat, feeling poor, activity limitation and use of cough/cold medications daily; and cough, sputum and abnormal lung examination at follow-up
Notes	Only 20% of eligible patients enrolled in study (but unenrolled not different clinically per chart review). 13 erythromycin volunteers dropped out due to gastrointestinal (GI) side effects

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) All outcomes	Low risk	
Blinding (performance bias and detection bias)	Low risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Unclear risk	Not reported
Other bias	Low risk	

Evans 2002

Methods	Double-blinded RCT
Participants	220 adults (aged 18 to 88) with cough (with or without sputum) of 2 to 14 days duration
Interventions	Azithromycin 500 mg on day 1 and 250 mg daily on days 2 to 5 versus vitamin C 500 mg on day 1 and 250 mg daily on days 2 to 5 (total dose 1.5 G)
Outcomes	Acute bronchitis health-related quality of life on day 3 and 7, proportion of participants who had returned to usual daily activities on days 3 and 7, side effects on days 3 and 7

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Evans 2002 (*Continued*)

Notes	88% of eligible population included. Both groups received cough suppressant (dextromethorphan) and albuterol inhaler. No difference between groups in the use of albuterol inhaler at follow-up. 31/220 (14%) lost to follow-up. Timing of outcome at day 3 and day 7 (day 7 taken as outcome time in this review). Study was stopped by data-monitoring and safety committee because "outcomes were equivalent and there was sufficient precision to be confident that the likelihood of detecting a clinically meaningful difference with a larger sample was so small that continued enrolment of patients would be inappropriate"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) All outcomes	Low risk	
Blinding (performance bias and detection bias)	Low risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Unclear risk	Not reported
Other bias	Low risk	

Franks 1984

Methods	Double-blinded RCT
Participants	67 patients aged 14 or older with less than 15 days of productive cough (in the absence of clinical pneumonitis). Excluded if could not produce sputum specimen for Gram stain. Drop-outs = 13/67
Interventions	Trimethoprim-sulfamethoxazole (160/800) BID for 7 days versus identical appearing placebo. Patients kept daily symptom logs. No follow-up visit
Outcomes	Cough, night cough, sputum production, general well-being, fever, work disability, use of adjunctive medications and side effects
Notes	No mention of per cent of eligible patients who refused enrolment

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Franks 1984 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) All outcomes	Low risk	
Blinding (performance bias and detection bias)	Low risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Unclear risk	Not reported
Other bias	Low risk	

Howie 1970

Methods	Double-blinded RCT
Participants	164 patients with a productive cough in conjunction with a cold or influenza-like illness that was not resolving after 2 days
Interventions	Self-treatment with demethyl chlortetracycline (300 mg) or placebo BID for 5 days. Patients kept daily symptom logs. No initial or follow-up visits
Outcomes	Duration of and presence on day 5 of cough, productive cough and purulent sputum; and duration of time off work
Notes	This was unpublished data about a subgroup of people with a cold or influenza-like illness; total number of people who treated themselves for a single episode of illness and returned symptom cards = 301

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Low risk	

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Howie 1970 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Low risk	
Blinding (performance bias and detection bias)	Low risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Unclear risk	Not reported
Other bias	Low risk	

Hueston 1994

Methods	Double-blinded RCT
Participants	23 adults (aged 18 to 65 years), with productive cough of less than 30 days duration and no clinical evidence of pneumonia. Drop-outs = 0
Interventions	Erythromycin (250 mg) QID for 10 days versus identical-looking placebo. Patients kept daily symptom log and were re-examined on day 7 or 8
Outcomes	Cough, night cough, ability to perform normal work and general well-being daily and at follow-up; overall use of over-the-counter medications and side effects; and abnormal lung exam at follow-up
Notes	This was part of a 2 x 2 designed study comparing erythromycin + albuterol inhaler versus erythromycin + placebo versus albuterol inhaler + placebo versus placebo + placebo. The data extracted for this review were unpublished and limited to the erythromycin + placebo group versus the placebo + placebo group

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	
Blinding (performance bias and detection bias)	Unclear risk	Not reported

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Hueston 1994 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Unclear risk	Not reported
Other bias	Unclear risk	Not reported

Kaiser 1996

Methods	Double-blinded RCT
Participants	75 patients (aged 16 to 64) with common cold and concomitant non-purulent tracheobronchitis and no evidence of sinusitis, pharyngitis, purulent bronchitis or pneumonia. Mean duration of illness 3 days
Interventions	Amoxicillin-clavulanic acid (375 mg TID for 5 days) versus identical-looking placebo. Patients re-evaluated on days 5 to 7
Outcomes	Persistent or worse symptoms versus cure at follow-up
Notes	These were unpublished data about a subgroup of patients in a study of patients with common cold; total number of patients in study was 307

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) All outcomes	Low risk	
Blinding (performance bias and detection bias)	Low risk	
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Unclear risk	Not reported
Other bias	Low risk	

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

King 1996

Methods	Double-blinded RCT
Participants	91 patients (age 8 or older) with cough and sputum for up to 2 weeks, and no signs of sinusitis, otitis or pneumonia and no localised abnormal lung exam. All tested for *Mycoplasma* (one-half with negative serology excluded)
Interventions	Erythromycin (250 mg QID for 10 days) versus identical-looking placebo. Volunteers kept daily logs and returned for follow-up visit at day 14 to 18
Outcomes	Cough, chest congestion, use of cough medication, general well-being, sleep and normal activities
Notes	No mention of eligible patients who refused to volunteer

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) All outcomes	Low risk	
Blinding (performance bias and detection bias)	Low risk	
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Unclear risk	Not reported
Other bias	High risk	

Little 2005

Methods	RCT
Participants	426, subgroup of 807 patients with acute uncomplicated lower respiratory tract infection. Inclusion criteria: aged 3 or more with uncomplicated LRTI for less than 21 days with cough as main symptom and at least 1 of sputum, chest pain, dyspnoea and wheeze
Interventions	6-arm RCT: (1) no leaflet or antibiotic; (2) immediate antibiotics plus leaflet; (3) immediate antibiotics and no leaflet; (4) leaflet only; (5) leaflet and delayed antibiotic; (6) no leaflet and delayed antibiotics. Only data from the no treatment and immediate antibiotic groups included in the analysis. The antibiotic used was amoxicillin 250 mg TDS

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Little 2005 (*Continued*)

	for 10 days (125 mg if less than 10 years) or erythromycin 250 mg QDS if penicillin allergic
Outcomes	Daily diary for 3 weeks recording antipyretic use and 6 symptoms (cough dyspnoea, sputum production, well-being, sleep disturbance and activity disturbance); satisfaction questionnaire; belief in antibiotics scale; reported antibiotic use; note review for re-consultation
Notes	25% lost to follow-up in no treatment and immediate antibiotic arms

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) All outcomes	High risk	Open design
Blinding (performance bias and detection bias)	High risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Unclear risk	Not reported
Other bias	Low risk	

Little 2013

Methods	RCT
Participants	2061 patients aged 18 or over presenting with lower respiratory tract infection with cough duration less than 28 days
Interventions	Amoxicillin 1g 3 times daily for 7 days
Outcomes	Duration of symptoms rated as moderately bad or worsening; mean symptom severity on days 2 to 4; proportion with symptoms resolved on day 7; new or worsening symptoms presenting clinically to GPs and adverse effects
Notes	Adequately powered for subgroup analysis of patients aged over 60 (n = 595)

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Little 2013 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) All outcomes	Low risk	Clinicians, patients and outcome assessors all blinded
Blinding (performance bias and detection bias)	Low risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	88% follow-up in both intervention and control groups
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Llor 2013

Methods	RCT (3 arms)
Participants	420 patients age 18 to 70 years presenting with respiratory tract infection of 1 week evolution with cough as the predominant symptom. We included data from the antibiotic arm (137 patients) and the placebo arm (143 patients)
Interventions	Ibuprofen or co-amoxiclav (dose 500 mg/125 mg)
Outcomes	Number days with frequent cough defined using a symptom diary. Secondary outcomes included clinically improved or cured, time to symptom resolution, median days with cough and adverse effects
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Patients were randomised using a random number table into 3 blocks
Allocation concealment (selection bias)	Low risk	Patients were unaware of allocation and clinicians gave patients sealed containers so also unaware of allocation

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Llor 2013 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Low risk	Patients blinded and described as single-blind study. Tablets placed in sealed containers before dispatch by an independent pharmacist
Blinding (performance bias and detection bias)	Low risk	Outcomes collected in symptom diaries not seen by the investigators
Incomplete outcome data (attrition bias) All outcomes	Low risk	> 90% follow-up
Selective reporting (reporting bias)	Low risk	Protocol available
Other bias	Unclear risk	Not reported

Matthys 2000

Methods	Double-blinded RCT
Participants	294, a subgroup of 676 patients, mean age 39 (range 18 to 79 with acute bronchitis. Inclusion criteria: aged 18 years or older, symptoms of recent onset within last 5 days, nightly cough as main symptom (without at least 4 awakenings during the night) and without reduced FEV1 (more than 75% normal)
Interventions	4-arm RCT: (1) myrtol standardised (phytotherapeutic extract); (2) cefuroxime 500 mg BID; (3) ambroxol (mucolytic agent); (4) placebo capsules. Only data from cefuroxime and placebo arms included in the analysis
Outcomes	Daytime cough, night-time cough, type of cough and general well-being recorded by each participant; clinical examination at follow-up; "overall efficacy" judge by physician and participant; bronchial hyperreactivity; change in lung function; number of patients with relapse within 4 weeks; side effects. Physician assessment at 7 and 14 days; diary data on 3 follow-up time periods: day 7, 14, 15 to 28
Notes	Secretolytics, mucolytics and antitussives prohibited during the study. Multiple hypothesis testing for all 4 treatment groups. 3/343 (0.9%) lost to follow-up

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias)	Low risk	

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Matthys 2000 (*Continued*)

All outcomes		
Blinding (performance bias and detection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Unclear risk	Not reported
Other bias	Low risk	

Nduba 2008

Methods	Triple-blind, placebo-controlled RCT
Participants	529 of 660 patients, mean age 31; 55% female. Productive cough for < 2 weeks, no serious medical co-morbidity and no antibiotic treatment in previous 2 weeks. All patients had HIV test and CXR at baseline. Excluded if CXR showed pneumonia or TB
Interventions	Amoxicillin 500 mg TDS for 7 days versus identical placebo tablet
Outcomes	Clinical cure at 14 days as measured by > 75% reduction in Acute Bronchitis Severity Score
Notes	Reported as first study of acute bronchitis treatment that used an equivalence design. Data available for HIV-positive patients but not included in the review

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The patients were randomised independently using a random number generator
Allocation concealment (selection bias)	Low risk	Antibiotic or placebo tablets identical in appearance, taste and smell were place in identical sealed opaque containers identifiable only with a unique study identifier
Blinding (performance bias and detection bias) All outcomes	Low risk	All clinical and research staff were blinded to the allocation of participants and the allocation schedule was kept in the office of the Chief Research Pharmacist in the host institution
Blinding (performance bias and detection bias)	Low risk	

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Incomplete outcome data (attrition bias) All outcomes	Low risk	> 85% follow-up for outcome data
Selective reporting (reporting bias)	Unclear risk	No access to original protocol though selective reporting not apparent from trial description
Other bias	Low risk	

Scherl 1987

Methods	Double-blinded RCT
Participants	39 patients (older than 12 years old) with chief complaint of cough with purulent sputum and without: other known bacterial infection, flu-like syndrome, chief complaint of coryza or sore throat with minimal sputum, or chest radiograph consistent with pneumonia (not all had radiographs). Drop-outs = 8/31
Interventions	Doxycycline (100 mg BID on day 1 and 100 mg QID on days 2 to 7) versus placebo. Kept daily symptom log and had follow-up visit at day 14
Outcomes	Cough, sputum, feverishness, days missed from work or normal activity, chest pain, dyspnoea, side effects
Notes	No mention of eligible patients who refused to volunteer

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) All outcomes	Low risk	
Blinding (performance bias and detection bias)	Low risk	
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Unclear risk	Not reported
Other bias	Low risk	

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Stott 1976

Methods	Double-blinded RCT
Participants	212 patients aged > 14 years with cough and purulent sputum of up to 1 week. Excluded if chest exam was abnormal. Drop-outs = 5/212
Interventions	Patients given doxycycline or placebo (2 pills on day 1, then 1 daily for 9 days). Had follow-up after 1 week, if "satisfied with outcome" then treatment ended; if not, then completed remaining pills and continued to record symptoms. Volunteers completed daily symptom logs
Outcomes	Day cough, night cough, "yellow spit", "clear spit", "off color", runny nose, sore throat, general aches, headache, vomiting, off work daily and at follow-up; clinical impression at follow-up; and illnesses over next 6 months
Notes	No difference in average pill consumption between groups (9.3 in doxycycline group versus 9.2 in placebo group). No mention of eligible patients who refused to volunteer

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) All outcomes	Low risk	
Blinding (performance bias and detection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Unclear risk	Not reported
Other bias	Low risk	

Verheij 1994

Methods	Double-blinded RCT
Participants	158 adults (age 18 or older) with cough and purulent sputum, and no clinical sinusitis or pneumonia. Drop-outs = 13/158

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Verheij 1994 (*Continued*)

Interventions	Doxycycline (200 mg on day 1 and 100 mg on days 2 to 10) versus placebo. Volunteers kept daily symptom log, and had follow-up visit on day 11
Outcomes	Day cough, night cough, productive cough, feeling ill, impairment of activities and side effects daily; and clinical impression and auscultatory abnormalities at follow-up
Notes	158/209 eligible patients entered study (no difference in age, sex or main symptoms between volunteers and unenrolled)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) All outcomes	Low risk	
Blinding (performance bias and detection bias)	Low risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Unclear risk	Not reported
Other bias	Low risk	

Williamson 1984

Methods	Double-blinded RCT
Participants	74 adults (age 21 to 65) with cough and sputum, and concurrent upper respiratory tract infection, rhonchi, or history of fever; excluded for temperature more than 39.5, signs or symptoms of sinus infection, or chest radiograph with consolidation (but not ordered on all). Drop-outs = 5/74
Interventions	Doxycycline (100 mg BID on day 1, then 100 mg QID on days 2 to 7) versus identical-looking placebo. Kept daily symptom log, returned for follow-up visit on day 7 to 10. If not improved at follow-up, could get antibiotic prescription
Outcomes	General well-being, bother of cough, night cough, activity limitation, feverishness, sputum colour daily, doses of antitussives and clinical impression at follow-up

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Williamson 1984 (*Continued*)

Notes	No mention of eligible patients who refused to volunteer	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) All outcomes	Low risk	
Blinding (performance bias and detection bias)	Low risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Unclear risk	Not reported
Other bias	Unclear risk	Not reported

BID: twice a day
CXR: chest X-ray
FEV1: forced expiratory volume in one second
LRTI: lower respiratory tract infection
QID: four times a day
QDS: four times a day
RCT: randomised controlled trial
TB: tuberculosis
TDS: three times a day
TID: three times a day

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Bateiha 2002	185 patients with acute respiratory tract infection from 2 health centres in Jordan. Assignment to antibiotic (azithromycin) was by means of alternation, not randomisation. At follow-up of 3 days, 1 week and 2 weeks, patients administered azithromycin or placebo did similarly in terms of the proportions improved or cured and in terms of duration of illness. The authors of the study conclude that routine use of antibiotics (azithromycin)

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

(*Continued*)

	in acute respiratory tract infection is unlikely to alter the course of the illness
Christ-Crain 2004	RCT concerned with application of a diagnostic test (serum calcitonin precursor, procalcitonin) which is raised in bacterial infections. 243 patients admitted to hospital with suspected lower respiratory tract infections were randomly assigned standard care (standard group; n = 119) or procalcitonin-guided treatment (procalcitonin group; n = 124). On the basis of serum procalcitonin concentrations, use of antibiotics was more or less discouraged (< 0.1 µG/L or < 0.25 µG/L) or encouraged (greater than or equal to 0.5 µG/L or greater than or equal to 0.25 µG/L), respectively. Re-evaluation was possible after 6 to 24 hours in both groups. Primary endpoint was use of antibiotics. 59 (24%) has diagnosis of "acute bronchitis". Antibiotic use decreased in the procalcitonin group. Withholding antibiotic treatment based on procalcitonin measurement did not compromise patient outcome
Dowell 2001	RCT of "delayed" versus "immediate" antibiotics for acute cough. Patients randomised to "delayed" arm were asked to wait a week before collecting their prescription. 55% of patients did not pick up their prescription. More patients were satisfied and "enabled" in the immediate treatment arm
Gordon 1974	Participants were children with "symptoms referable to the respiratory tract", therefore likely many had upper respiratory infections (78% to 96% had runny nose, 74% to 83% had inflamed nasal mucosa)
Gottfarb 1994	Post-randomisation exclusion of 23% of the sample because of laboratory evidence of pertussis infection. Outcomes not clearly reported. Inclusion criterion was cough, but not sputum production (therefore not consistent with definition used in the other studies). Age of participants in this study was 7 months to 7 years: the minimum age in the other studies was 8 (King 1996), 12 (Scherl 1987), or 14 or older (remaining studies)
Stephenson 1989	Participants were adults with upper respiratory infection. Not all had cough, and no information available on the subgroup of patients with productive cough
Thomas 1978	Explicit data from the study were not published and the data are no longer available

RCT: randomised controlled trial

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

DATA AND ANALYSES

Comparison 1. Cough at follow-up visit

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of patients with cough	4	275	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.49, 0.85]

Comparison 2. Night cough at follow-up visit

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of patients with night cough	4	538	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.54, 0.83]

Comparison 3. Productive cough at follow-up visit

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of patients with productive cough	7	713	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.82, 1.16]
1.1 Acute bronchitis studies	6	549	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.72, 1.08]
1.2 Subgroup with productive cough from URTI study	1	164	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [0.88, 1.75]

Comparison 4. Days of cough

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean number of days of cough	7	2776	Mean Difference (IV, Fixed, 95% CI)	-0.46 [-0.87, -0.04]
1.1 Acute bronchitis studies	6	2350	Mean Difference (IV, Fixed, 95% CI)	-0.55 [1.00, -0.10]
1.2 Subgroup with no placebo control	1	426	Mean Difference (IV, Fixed, 95% CI)	0.11 [-1.01, 1.23]

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Comparison 5. Days of productive cough

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean number of days of productive cough	6	699	Mean Difference (IV, Fixed, 95% CI)	-0.43 [-0.93, 0.07]
1.1 Acute bronchitis studies	5	535	Mean Difference (IV, Fixed, 95% CI)	-0.52 [-1.03, -0.01]
1.2 Subgroup with productive cough from URTI study	1	164	Mean Difference (IV, Fixed, 95% CI)	1.04 [-1.04, 3.12]

Comparison 6. Clinically improved

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of patients reporting no activity limitations or described as cured/globally improved	11	3841	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.99, 1.15]

Comparison 7. Limitation in work or activities at follow-up visit

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of patients with limitations	5	478	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.46, 1.22]

Comparison 8. Days of feeling ill

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean number of days of feeling ill	5	809	Mean Difference (IV, Fixed, 95% CI)	-0.64 [-1.16, -0.13]
1.1 Acute bronchitis studies	4	435	Mean Difference (IV, Fixed, 95% CI)	-0.58 [-1.16, -0.00]
1.2 Subgroup with no placebo control	1	374	Mean Difference (IV, Fixed, 95% CI)	-0.86 [-1.97, 0.25]

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Comparison 9. Days of impaired activities

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean number of days of impaired activities	6	767	Mean Difference (IV, Fixed, 95% CI)	-0.49 [-0.94, -0.04]
1.1 Acute bronchitis studies	5	393	Mean Difference (IV, Fixed, 95% CI)	-0.48 [-0.96, 0.01]
1.2 Subgroup with no placebo control	1	374	Mean Difference (IV, Fixed, 95% CI)	-0.57 [-1.75, 0.61]

Comparison 10. Not improved by physician's global assessment at follow-up visit

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of patients not improved	6	891	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.48, 0.79]
1.1 Acute bronchitis studies	5	816	Risk Ratio (M-H, Fixed, 95% CI)	0.44 [0.30, 0.65]
1.2 Subgroup with non-purulent tracheobronchitis from URTI study	1	75	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.82, 1.29]

Comparison 11. Abnormal lung exam at follow-up visit

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of patients with abnormal lung exams	5	613	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.41, 0.70]

Comparison 12. Adverse effects

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of patients with adverse effects	12	3496	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [1.05, 1.36]
1.1 Acute bronchitis studies	11	3162	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [1.07, 1.40]
1.2 Subgroup with no placebo control	1	334	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.61, 1.50]

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Analysis 1.1. Comparison 1 Cough at follow-up visit, Outcome 1 Number of patients with cough.

Review: Antibiotics for acute bronchitis

Comparison: 1 Cough at follow-up visit

Outcome: 1 Number of patients with cough

Study or subgroup	Antibiotic n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Dunlay 1987	14/23	18/22		26.4 %	0.74 [0.51, 1.09]
Hueston 1994	8/11	6/9		9.5 %	1.09 [0.61, 1.96]
Verheij 1994	15/70	26/67		38.1 %	0.55 [0.32, 0.95]
Williamson 1984	10/39	17/34		26.0 %	0.51 [0.27, 0.96]
Total (95% CI)	**143**	**132**		**100.0 %**	**0.64 [0.49, 0.85]**

Total events: 47 (Antibiotic), 67 (Placebo)

Heterogeneity: $Chi^2 = 4.47$, df = 3 (P = 0.22); $I^2 = 33\%$

Test for overall effect: Z = 3.16 (P = 0.0016)

Test for subgroup differences: Not applicable

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Analysis 2.1. Comparison 2 Night cough at follow-up visit, Outcome 1 Number of patients with night cough.

Review: Antibiotics for acute bronchitis

Comparison: 2 Night cough at follow-up visit

Outcome: 1 Number of patients with night cough

Study or subgroup	Antibiotic n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Dunlay 1987	7/21	14/24		11.0 %	0.57 [0.29, 1.14]
Hueston 1994	2/10	2/8		1.9 %	0.80 [0.14, 4.49]
Matthys 2000	63/171	96/169		81.1 %	0.65 [0.51, 0.82]
Verheij 1994	8/69	7/66		6.0 %	1.09 [0.42, 2.85]
Total (95% CI)	**271**	**267**		**100.0 %**	**0.67 [0.54, 0.83]**

Total events: 80 (Antibiotic), 119 (Placebo)

Heterogeneity: $Chi^2 = 1.32$, df = 3 (P = 0.72); $I^2 = 0.0\%$

Test for overall effect: Z = 3.62 (P = 0.00030)

Test for subgroup differences: Not applicable

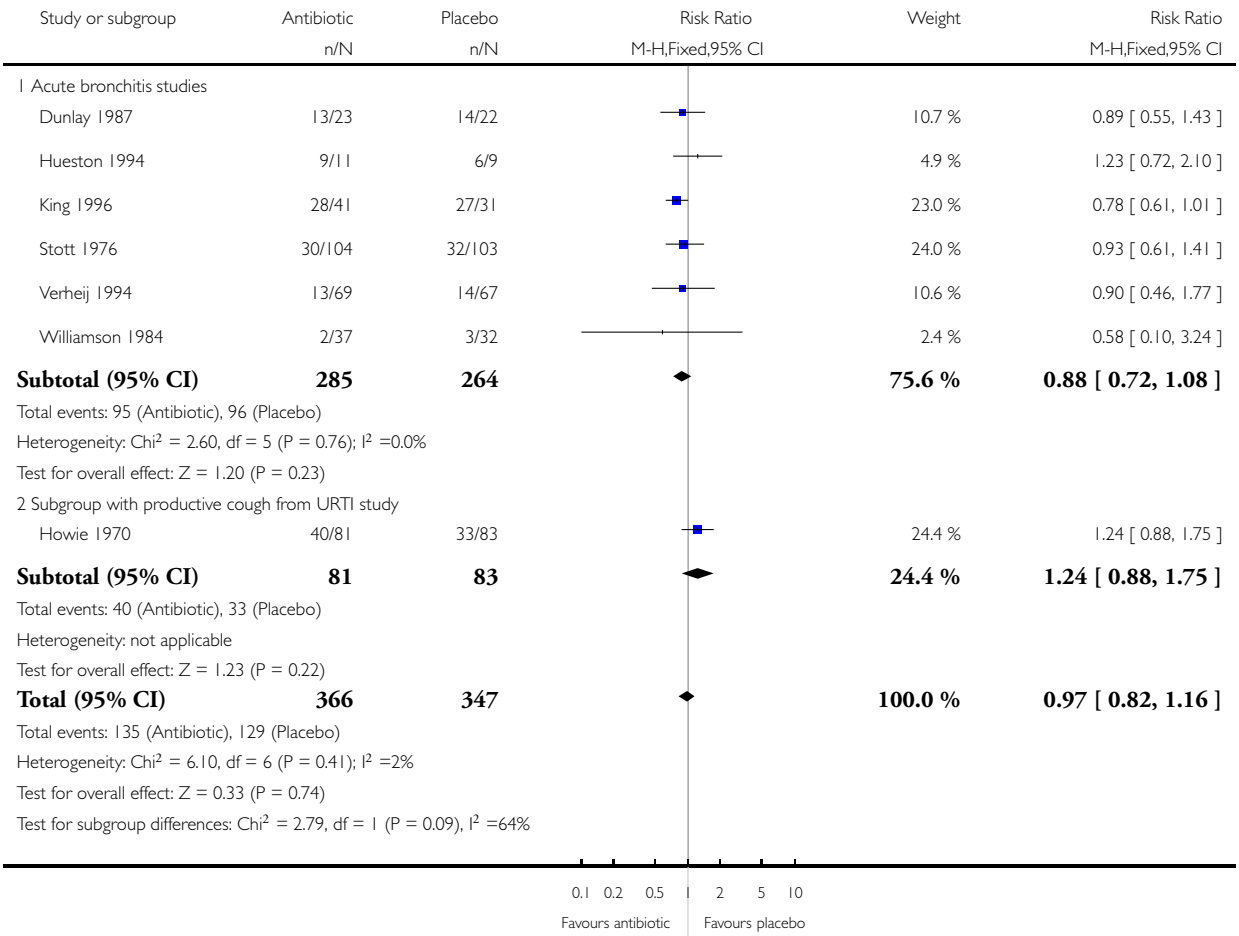
Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Analysis 3.1. Comparison 3 Productive cough at follow-up visit, Outcome 1 Number of patients with productive cough.

Review: Antibiotics for acute bronchitis

Comparison: 3 Productive cough at follow-up visit

Outcome: 1 Number of patients with productive cough



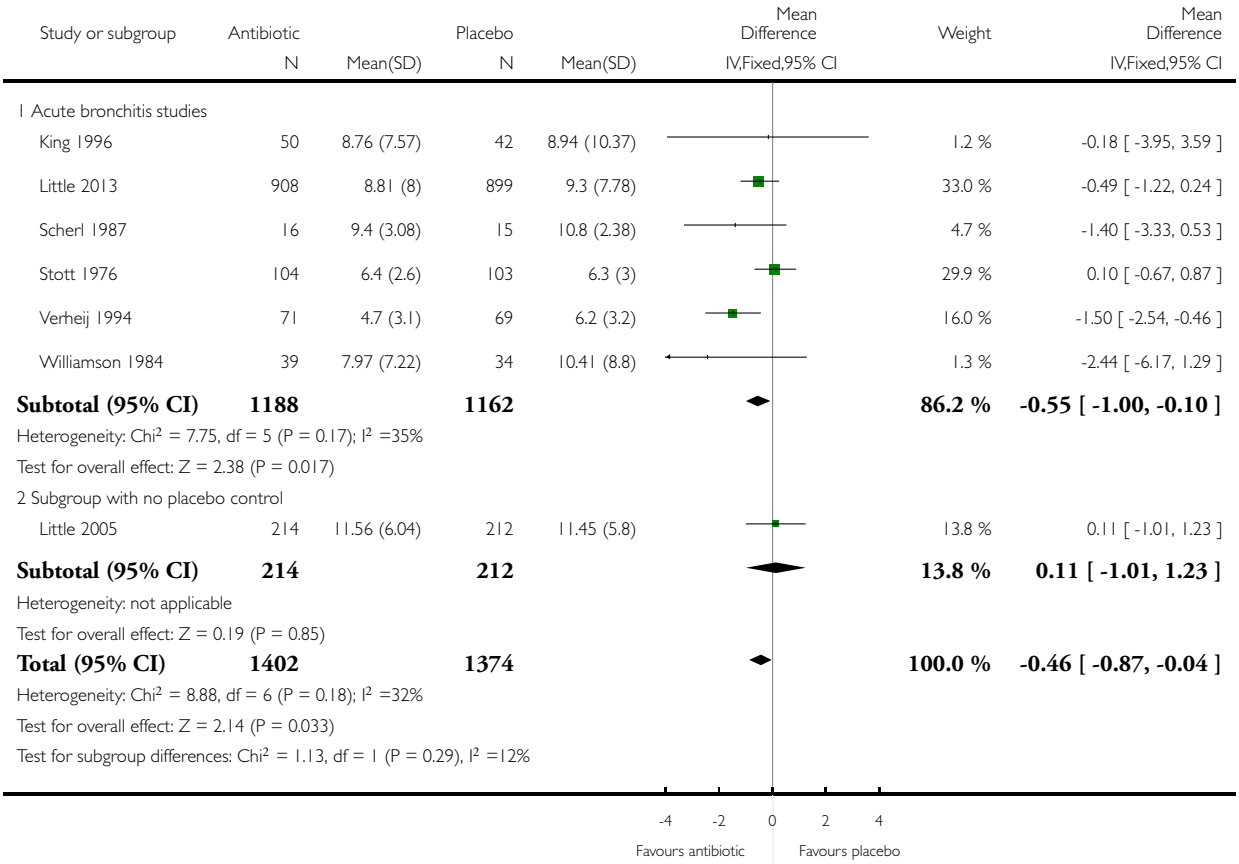
Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Analysis 4.1. Comparison 4 Days of cough, Outcome 1 Mean number of days of cough.

Review: Antibiotics for acute bronchitis

Comparison: 4 Days of cough

Outcome: 1 Mean number of days of cough



Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

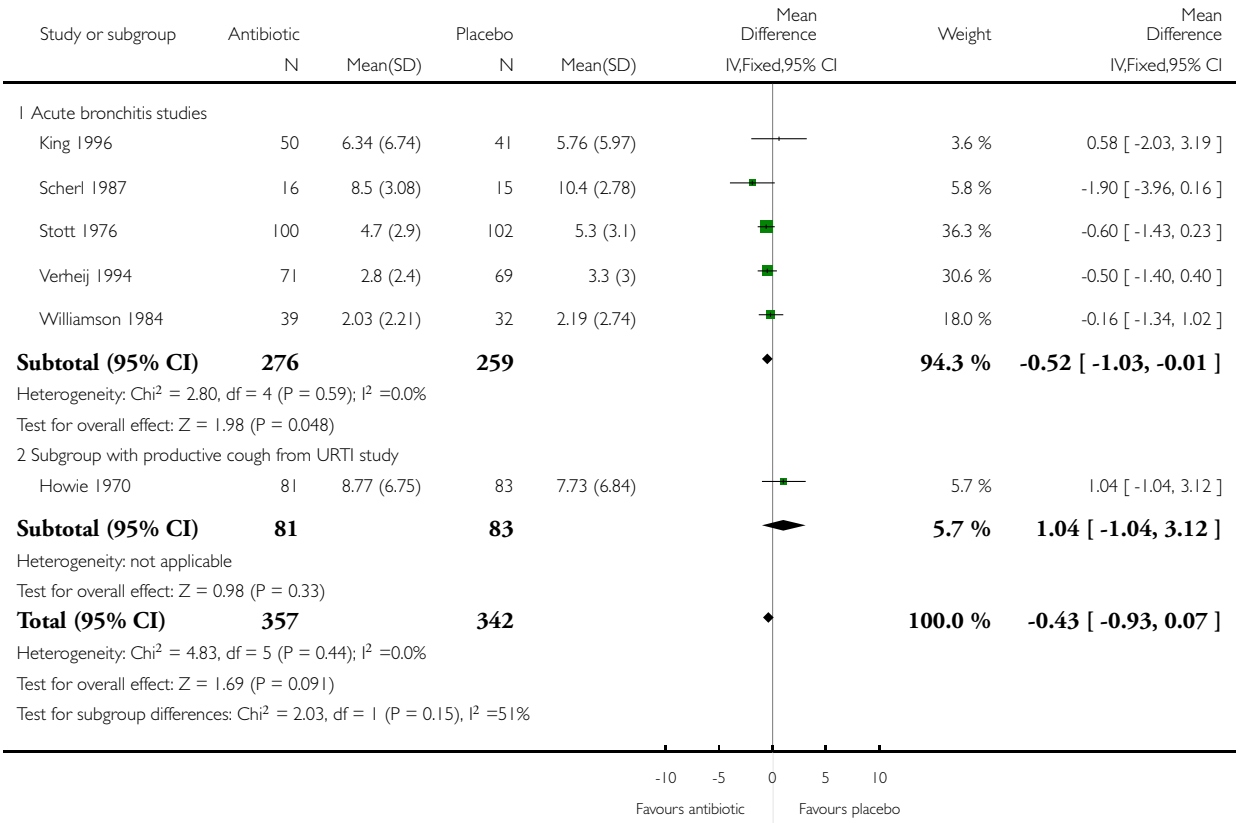
Analysis 5.1. Comparison 5 Days of productive cough, Outcome 1 Mean number of days of productive cough.

Review: Antibiotics for acute bronchitis

Comparison: 5 Days of productive cough

Outcome: 1 Mean number of days of productive cough

Study or subgroup	Antibiotic N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Acute bronchitis studies							
King 1996	50	6.34 (6.74)	41	5.76 (5.97)		3.6 %	0.58 [-2.03, 3.19]
Scherl 1987	16	8.5 (3.08)	15	10.4 (2.78)		5.8 %	-1.90 [-3.96, 0.16]
Stott 1976	100	4.7 (2.9)	102	5.3 (3.1)		36.3 %	-0.60 [-1.43, 0.23]
Verheij 1994	71	2.8 (2.4)	69	3.3 (3)		30.6 %	-0.50 [-1.40, 0.40]
Williamson 1984	39	2.03 (2.21)	32	2.19 (2.74)		18.0 %	-0.16 [-1.34, 1.02]
Subtotal (95% CI)	**276**		**259**			**94.3 %**	**-0.52 [-1.03, -0.01]**
Heterogeneity: Chi^2 = 2.80, df = 4 (P = 0.59); I^2 =0.0%							
Test for overall effect: Z = 1.98 (P = 0.048)							
2 Subgroup with productive cough from URTI study							
Howie 1970	81	8.77 (6.75)	83	7.73 (6.84)		5.7 %	1.04 [-1.04, 3.12]
Subtotal (95% CI)	**81**		**83**			**5.7 %**	**1.04 [-1.04, 3.12]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.98 (P = 0.33)							
Total (95% CI)	**357**		**342**			**100.0 %**	**-0.43 [-0.93, 0.07]**
Heterogeneity: Chi^2 = 4.83, df = 5 (P = 0.44); I^2 =0.0%							
Test for overall effect: Z = 1.69 (P = 0.091)							
Test for subgroup differences: Chi^2 = 2.03, df = 1 (P = 0.15), I^2 =51%							



Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Analysis 6.1. Comparison 6 Clinically improved, Outcome 1 Number of patients reporting no activity limitations or described as cured/globally improved.

Review: Antibiotics for acute bronchitis

Comparison: 6 Clinically improved

Outcome: 1 Number of patients reporting no activity limitations or described as cured/globally improved

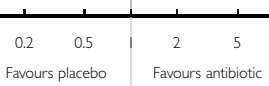
Study or subgroup	Antibiotic n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Stott 1976	94/104	86/103		10.7 %	1.08 [0.97, 1.20]
Franks 1984	14/19	17/29		2.7 %	1.26 [0.84, 1.89]
Williamson 1984	35/37	31/32		11.0 %	0.98 [0.88, 1.08]
Brickfield 1986	21/26	14/24		2.9 %	1.38 [0.94, 2.04]
Dunlay 1987	19/20	20/23		7.3 %	1.09 [0.91, 1.32]
Verheij 1994	64/73	55/72		8.6 %	1.15 [0.98, 1.34]
Matthys 2000	158/171	136/172		11.5 %	1.17 [1.07, 1.28]
Evans 2002	86/97	82/92		10.9 %	0.99 [0.90, 1.10]
Nduba 2008	270/330	277/330		12.2 %	0.97 [0.91, 1.04]
Llor 2013	107/137	123/143		10.5 %	0.91 [0.81, 1.01]
Little 2013	539/908	436/899		11.6 %	1.22 [1.12, 1.33]
Total (95% CI)	**1922**	**1919**		**100.0 %**	**1.07 [0.99, 1.15]**

Total events: 1407 (Antibiotic), 1277 (Placebo)

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 42.49$, df = 10 ($P<0.00001$); $I^2 = 76\%$

Test for overall effect: Z = 1.77 (P = 0.077)

Test for subgroup differences: Not applicable



Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Analysis 7.1. Comparison 7 Limitation in work or activities at follow-up visit, Outcome 1 Number of patients with limitations.

Review: Antibiotics for acute bronchitis

Comparison: 7 Limitation in work or activities at follow-up visit

Outcome: 1 Number of patients with limitations

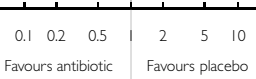
Study or subgroup	Antibiotic n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Dunlay 1987	1/20	3/23		8.8 %	0.38 [0.04, 3.40]
Evans 2002	11/97	10/92		32.4 %	1.04 [0.47, 2.34]
Franks 1984	5/19	12/29		30.0 %	0.64 [0.27, 1.52]
Verheij 1994	6/67	9/65		28.8 %	0.65 [0.24, 1.71]
Williamson 1984	0/36	0/30			Not estimable
Total (95% CI)	**239**	**239**		**100.0 %**	**0.75 [0.46, 1.22]**

Total events: 23 (Antibiotic), 34 (Placebo)

Heterogeneity: $Chi^2 = 1.23$, df = 3 (P = 0.75); $I^2 = 0.0\%$

Test for overall effect: Z = 1.16 (P = 0.25)

Test for subgroup differences: Not applicable



Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

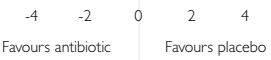
Analysis 8.1. Comparison 8 Days of feeling ill, Outcome 1 Mean number of days of feeling ill.

Review: Antibiotics for acute bronchitis

Comparison: 8 Days of feeling ill

Outcome: 1 Mean number of days of feeling ill

Study or subgroup	Antibiotic N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Acute bronchitis studies							
King 1996	25	3.92 (4.24)	27	3.67 (4.35)		4.9 %	0.25 [-2.09, 2.59]
Stott 1976	84	3.8 (2.2)	91	4.4 (2.7)		50.1 %	-0.60 [-1.33, 0.13]
Verheij 1994	71	4.3 (3)	69	5.1 (3.5)		22.7 %	-0.80 [-1.88, 0.28]
Williamson 1984	37	20.1 (11.2)	31	18.5 (12.9)		0.8 %	1.60 [-4.20, 7.40]
Subtotal (95% CI)	**217**		**218**			**78.5 %**	**-0.58 [-1.16, 0.00]**
Heterogeneity: Chi^2 = 1.19, df = 3 (P = 0.76); I^2 =0.0%							
Test for overall effect: Z = 1.97 (P = 0.049)							
2 Subgroup with no placebo control							
Little 2005	194	8.12 (5.1)	180	8.98 (5.8)		21.5 %	-0.86 [-1.97, 0.25]
Subtotal (95% CI)	**194**		**180**			**21.5 %**	**-0.86 [-1.97, 0.25]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.52 (P = 0.13)							
Total (95% CI)	**411**		**398**			**100.0 %**	**-0.64 [-1.16, -0.13]**
Heterogeneity: Chi^2 = 1.38, df = 4 (P = 0.85); I^2 =0.0%							
Test for overall effect: Z = 2.45 (P = 0.014)							
Test for subgroup differences: Chi^2 = 0.19, df = 1 (P = 0.66), I^2 =0.0%							



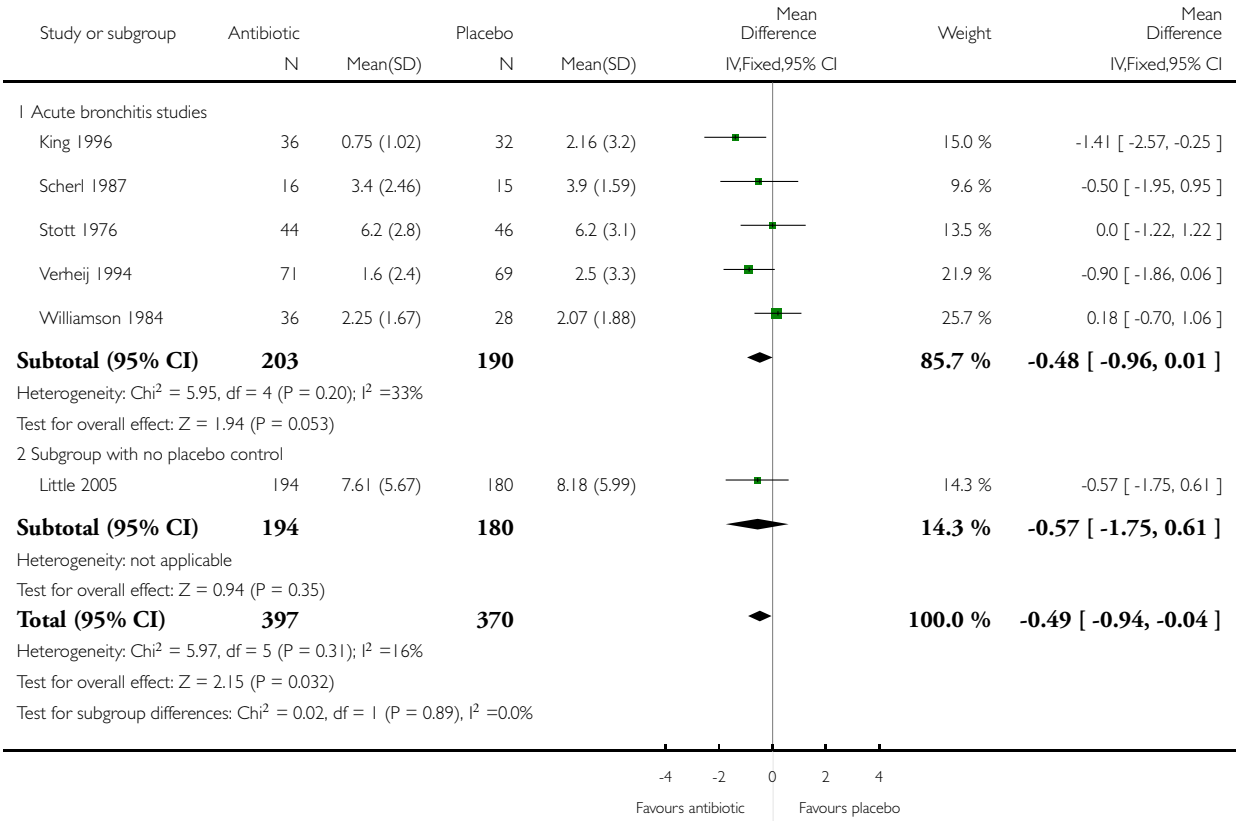
Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Analysis 9.1. Comparison 9 Days of impaired activities, Outcome 1 Mean number of days of impaired activities.

Review: Antibiotics for acute bronchitis

Comparison: 9 Days of impaired activities

Outcome: 1 Mean number of days of impaired activities



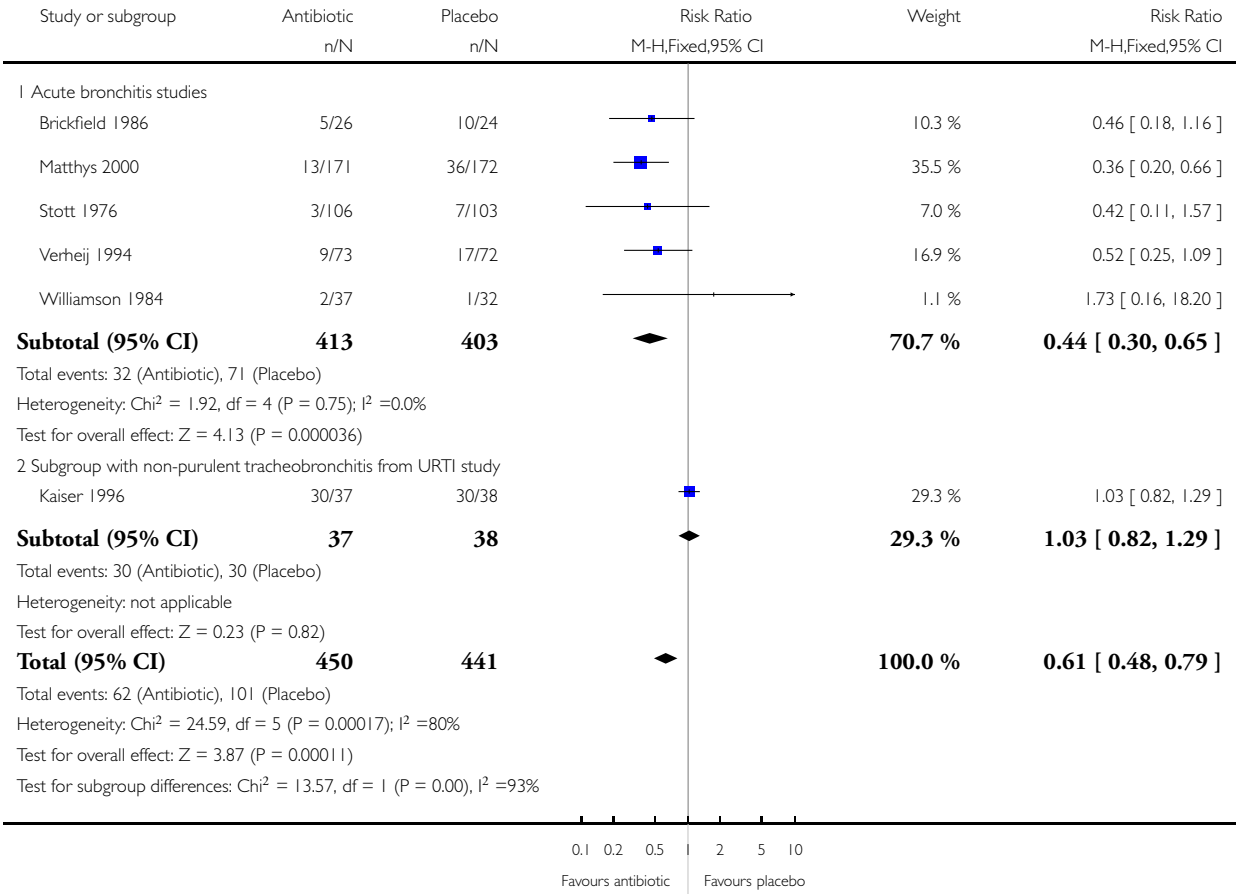
Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Analysis 10.1. Comparison 10 Not improved by physician's global assessment at follow-up visit, Outcome 1 Number of patients not improved.

Review: Antibiotics for acute bronchitis

Comparison: 10 Not improved by physician's global assessment at follow-up visit

Outcome: 1 Number of patients not improved



Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Analysis 11.1. Comparison 11 Abnormal lung exam at follow-up visit, Outcome 1 Number of patients with abnormal lung exams.

Review: Antibiotics for acute bronchitis

Comparison: 11 Abnormal lung exam at follow-up visit

Outcome: 1 Number of patients with abnormal lung exams

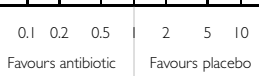
Study or subgroup	Antibiotic n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Dunlay 1987	0/23	6/22		6.2 %	0.07 [0.00, 1.24]
Hueston 1994	7/14	5/9		5.7 %	0.90 [0.41, 1.97]
Matthys 2000	46/171	83/172		77.8 %	0.56 [0.42, 0.75]
Verheij 1994	5/70	8/67		7.7 %	0.60 [0.21, 1.74]
Williamson 1984	0/36	2/29		2.6 %	0.16 [0.01, 3.25]
Total (95% CI)	**314**	**299**		**100.0 %**	**0.54 [0.41, 0.70]**

Total events: 58 (Antibiotic), 104 (Placebo)

Heterogeneity: $Chi^2 = 4.25$, df = 4 (P = 0.37); $I^2 = 6\%$

Test for overall effect: Z = 4.57 (P < 0.00001)

Test for subgroup differences: Not applicable



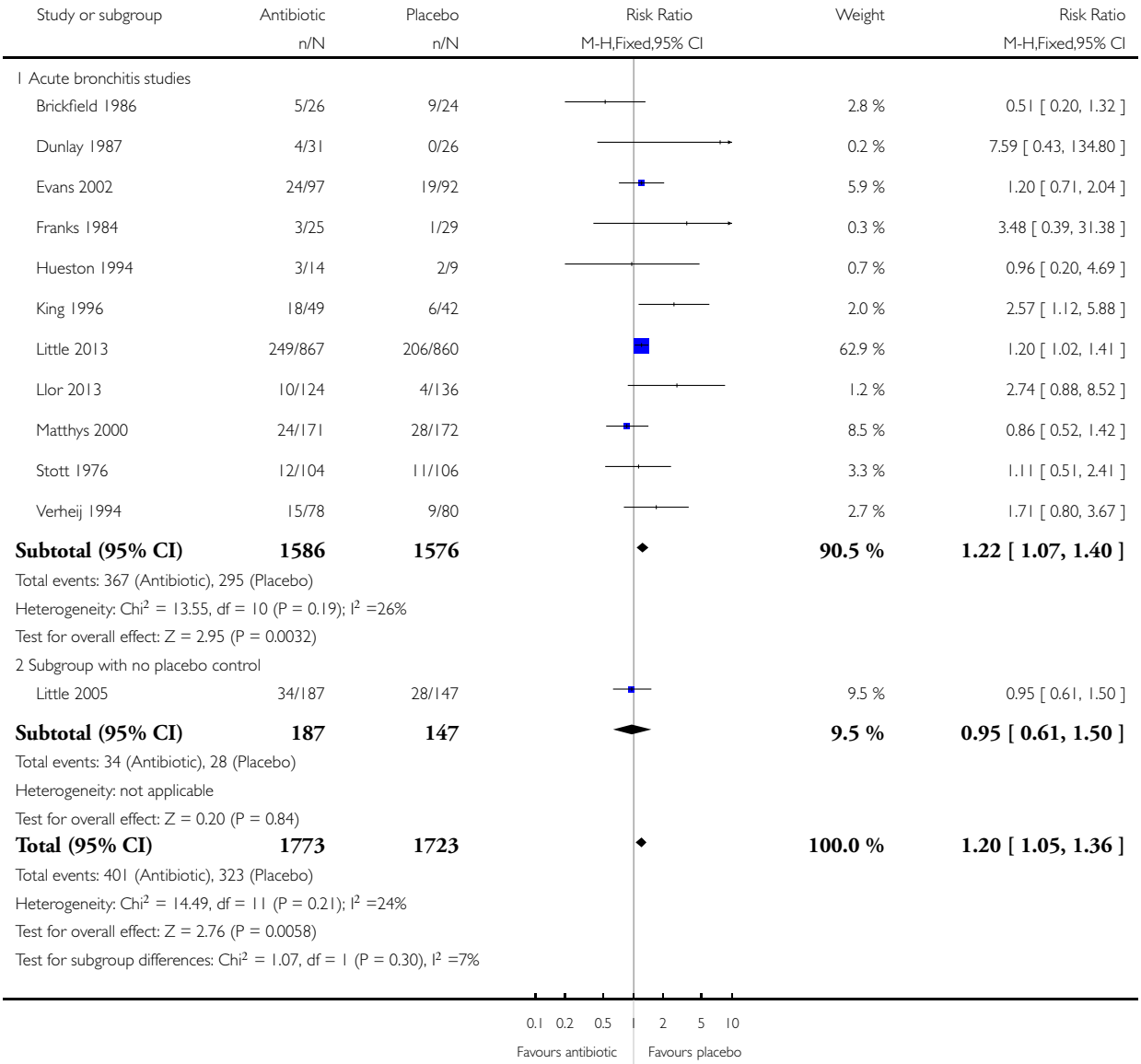
Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Analysis 12.1. Comparison 12 Adverse effects, Outcome 1 Number of patients with adverse effects.

Review: Antibiotics for acute bronchitis

Comparison: 12 Adverse effects

Outcome: 1 Number of patients with adverse effects



Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

APPENDICES

Appendix 1. MEDLINE (Ovid) and CENTRAL search strategy

1 exp Bronchitis/
2 bronchit*.tw.
3 (bronchial adj2 infect*).tw.
4 exp Respiratory Tract Infections/
5 or/1-4
6 exp Anti-Bacterial Agents/
7 exp Lactams/
8 exp Tetracyclines/
9 exp Aminoglycosides/
10 exp Glycopeptides/
11 exp Macrolides/
12 antibiotic*.tw.
13 (alamethicin or amdinocillin* or amikacin or amoxicillin* or ampicillin or aurodox or azithromycin or azlocillin or aztreonam or bacitracin or bacteriocin* or brefeldin* or butirosin* or candicidin or carbenicillin or carfecillin or cefaclor or cefadroxil or cefamandole or cefazolin or cefixime or cefmenoxime or cefmetazole or cefonicid or cefoperazone or cefotaxime or cefotetan or cefotiam or cefoxitin or cefsulodin or ceftazidime or ceftizoxime or ceftriaxone or cefuroxime or cephacetrile or cephalexin or cephaloglycin or cephaloridine or cephalosporin* or cephalothin or cephapirin or cephradine or chloramphenicol or chlortetracycline or citrinin or clarithromycin or clavulanic acid* or clindamycin or cloxacillin or colistin or cyclacillin or dactinomycin or daptomycin or demeclocycline or dibekacin or dicloxacillin or dihydrostreptomycin* or distamycin* or doxycycline or echinomycin or edeine or erythromycin* or floxacillin or framycetin or fusidic acid or gentamicin* or gramicidin or imipenem or lactam* or lasalocid or leucomycins or lymecycline or mepartricin or methacycline or methicillin or mezlocillin or mikamycin or minocycline or miocamycin or moxalactam or mupirocin or mycobacillin or nafcillin or nebramycin or enigericin or nisin or novobiocin or nystatin or ofloxacin or oligomycins or oxacillin or oxytetracycline or penicillanic acid or penicillic acid or penicillin* or piperacillin or pivampicillin or polymyxin* or pristinamycin* or prodigiosin or rifabutin or ristocetin or rolitetracycline or roxarsone or rutamycin or sirolimus or sisomicin or spectinomycin or streptogramin* or streptovaricin or sulbactam or sulbenicillin or talampicillin or teicoplanin or tetracycline or thiamphenicol or thiostrepton or ticarcillin or tobramycin or troleandomycin or tylosin or tyrocidine or tyrothricin or valinomycin or vancomycin or vernamycin* or viomycin* or virginiamycin* or beta-lactam*).tw,nm.
14 or/6-13
15 5 and 14
We combined the MEDLINE search with the Cochrane Highly Sensitive Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximising version (2008 revision); Ovid format (Lefebvre 2011).

Appendix 2. Embase.com search strategy

#2.24 #2.15 AND #2.23
#2.23 #2.18 NOT #2.22
#2.22 #2.19 NOT #2.21
#2.21 #2.19 AND #2.20
#2.20 'human'/de
#2.19 'animal'/de OR 'nonhuman'/de OR 'animal experiment'/de
#2.18 #2.16 OR #2.17
#2.17 random*:ab,ti OR placebo*:ab,ti OR crossover*:ab,ti OR 'cross over':ab,ti OR allocat*:ab,ti OR trial:ti OR (doubl* NEXT/1 blind*):ab,ti
#2.16 'randomized controlled trial'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp
#2.15 #2.5 AND #2.14
#2.14 #2.6 OR #2.7 OR #2.8 OR #2.9 OR #2.10 OR #2.11 OR #2.12 OR #2.13
#2.13 alamethicin:ab,ti OR amdinocillin*:ab,ti OR amikacin:ab,ti OR amoxicillin*:ab,ti OR ampicillin:ab,ti OR aurodox:ab,ti OR azithromycin:ab,ti OR azlocillin:ab,ti OR aztreonam:ab,ti OR bacitracin:ab,ti OR bacteriocin*:ab,ti OR brefeldin*:ab,ti OR butirosin*:

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ab,ti OR candicidin:ab,ti OR carbenicillin:ab,ti OR carfecillin:ab,ti OR cefaclor:ab,ti OR cefadroxil:ab,ti OR cefamandole:ab,ti OR cefazolin:ab,ti OR cefixime:ab,ti OR cefmenoxime:ab,ti OR cefmetazole:ab,ti OR cefonicid:ab,ti OR cefoperazone:ab,ti OR cefotaxime:ab,ti OR cefotetan:ab,ti OR cefotiam:ab,ti OR cefoxitin:ab,ti OR cefsulodin:ab,ti OR ceftazidime:ab,ti OR ceftizoxime:ab,ti OR ceftriaxone:ab,ti OR
cefuroxime:ab,ti OR cephacetrile:ab,ti OR cephalexin:ab,ti OR cephaloglycin:ab,ti OR cephaloridine:ab,ti OR cephalosporin*:ab,ti OR cephalothin:ab,ti OR cephapirin:ab,ti OR cephradine:ab,ti OR chloramphenicol:ab,ti OR chlortetracycline:ab,ti OR citrinin:ab,ti OR clarithromycin:ab,ti OR 'clavulanic acid':ab,ti OR clindamycin:ab,ti OR cloxacillin:ab,ti OR colistin:ab,ti OR cyclacillin:ab,ti OR dactinomycin:ab,ti OR daptomycin:ab,ti OR
demeclocycline:ab,ti OR dibekacin:ab,ti OR dicloxacillin:ab,ti OR dihydrostreptomycin*:ab,ti OR distamycin*:ab,ti OR doxycycline:ab,ti OR echinomycin:ab,ti OR edeine:ab,ti OR erythromycin*:ab,ti OR floxacillin:ab,ti OR framycetin:ab,ti OR 'fusidic acid':ab,ti OR gentamicin*:ab,ti OR gramicidin:ab,ti OR imipenem:ab,ti OR lactam*:ab,ti OR lasalocid:ab,ti OR leucomycins:ab,ti OR lymecycline:ab,ti OR mepartricin:ab,ti OR methacycline:ab,ti OR
methicillin:ab,ti OR mezlocillin:ab,ti OR mikamycin:ab,ti OR minocycline:ab,ti OR miocamycin:ab,ti OR moxalactam:ab,ti OR mupirocin:ab,ti OR mycobacillin:ab,ti OR nafcillin:ab,ti OR nebramycin:ab,ti OR enigericin:ab,ti OR nisin:ab,ti OR novobiocin:ab,ti OR nystatin:ab,ti OR ofloxacin:ab,ti OR oligomycins:ab,ti OR oxacillin:ab,ti OR oxytetracycline:ab,ti OR 'penicillanic acid':ab,ti OR 'penicillic acid':ab,ti OR penicillin*:ab,ti OR piperacillin:ab,ti OR pivampicillin:ab,ti OR polymyxin*:ab,ti OR pristinamycin*:ab,ti OR prodigiosin:ab,ti OR rifabutin:ab,ti OR ristocetin:ab,ti OR rolitetracycline:ab,ti OR roxarsone:ab,ti OR rutamycin:ab,ti OR sirolimus:ab,ti OR sisomicin:ab,ti OR spectinomycin:ab,ti OR streptogramin*:ab,ti OR streptovaricin:ab,ti OR sulbactam:ab,ti OR sulbenicillin:ab,ti OR talampicillin:ab,ti OR teicoplanin:ab,ti OR tetracycline:ab,ti OR thiamphenicol:ab,ti OR thiostrepton:ab,ti OR ticarcillin:ab,ti OR tobramycin:ab,ti OR troleandomycin:ab,ti OR tylosin:ab,ti OR tyrocidine:ab,ti OR tyrothricin:ab,ti OR valinomycin:ab,ti OR vancomycin:ab,ti OR vernamycin*:ab,ti OR viomycin*:ab,ti OR virginiamycin*:ab,ti OR 'beta-lactam':ab,ti OR 'beta-lactams':ab,ti
#2.12 antibiotic*:ab,ti
#2.11 'macrolide'/exp
#2.10 'glycopeptide'/de
#2.9 'aminoglycoside'/de
#2.8 'tetracycline derivative'/exp
#2.7 'lactam'/exp
#2.6 'antibiotic agent'/de
#2.5 #2.1 OR #2.2 OR #2.3 OR #2.4
#2.4 'respiratory tract infection'/de OR 'lower respiratory tract infection'/de
#2.3 (bronchial* NEAR/2 infect*):ab,ti
#2.2 bronchit*:ab,ti
#2.1 'bronchitis'/exp

Appendix 3. LILACS (BIREME) search strategy

(mh:bronchitis OR bronchit* OR bronquitis OR bronquite OR mh:c08.127.446* OR mh:c08.381.495.146* OR mh:c08.730.099* OR "bronchial infection" OR "bronchial infections" OR mh:"Respiratory Tract Infections" OR "respiratory tract infection" OR "respiratory tract infections" OR "Infecciones del Sistema Respiratorio" OR "Infecções Respiratórias") AND (mh:"Anti-Bacterial Agents" OR antibiotic* OR antibacterianos OR mh:d27.505.954.122.085* OR mh:lactams OR lactam* OR mh:d02.065.589* OR mh:d03.383.411* OR mh:tetracyclines OR tetracyclin* OR tetraciclinas OR mh:d02.455.426.559.847.562.900* OR mh:d04.615.562.900* OR mh:aminoglycosides OR aminoglicósidos OR aminoglicosídeos OR mh:d09.408.051* OR aminoglycoside* OR mh:glycopeptides OR glycopeptide* OR glicopéptidos OR glicopeptídeos OR mh:d09.400.420* OR mh:d12.644.233* OR mh:macrolides OR macrolide* OR macrólidos OR macrolídeos OR mh:d02.540.505* OR alamethicin OR amdinocillin* OR amikacin OR amoxicillin* OR ampicillin OR aurodox OR azithromycin OR azlocillin OR aztreonam OR bacitracin OR bacteriocin* OR brefeldin* OR butirosin* OR candicidin OR carbenicillin OR carfecillin OR cefaclor OR cefadroxil OR cefamandole OR cefazolin OR cefixime OR cefmenoxime OR cefmetazole OR cefonicid OR cefoperazone OR cefotaxime OR cefotetan OR cefotiam OR cefoxitin OR cefsulodin OR ceftazidime OR ceftizoxime OR ceftriaxone OR cefuroxime OR cephacetrile OR cephalexin OR cephaloglycin OR cephaloridine OR cephalosporin* OR cephalothin OR cephapirin OR cephradine OR chloramphenicol OR chlortetracycline OR citrinin OR clarithromycin OR "clavulanic acid" OR clindamycin OR cloxacillin OR colistin OR cyclacillin OR dactinomycin OR daptomycin OR demeclocycline OR dibekacin OR dicloxacillin OR dihydrostreptomycin* OR distamycin* OR doxycycline

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

OR echinomycin OR edeine OR erythromycin* OR floxacillin OR framycetin OR "fusidic acid" OR gentamicin* OR gramicidin OR imipenem OR lactam* OR lasalocid OR leucomycins OR lymecycline OR mepartricin OR methacycline OR methicillin OR mezlocillin OR mikamycin OR minocycline OR miocamycin OR moxalactam OR mupirocin OR mycobacillin OR nafcillin OR nebramycin OR enigericin OR nisin OR novobiocin OR nystatin OR ofloxacin OR oligomycins OR oxacillin OR oxytetracycline OR "penicillanic acid" OR "penicillic acid" OR penicillin* OR piperacillin OR pivampicillin OR polymyxin* OR pristinamycin* OR prodigiosin OR rifabutin OR ristocetin OR rolitetracycline OR roxarsone OR rutamycin OR sirolimus OR sisomicin OR spectinomycin OR streptogramin* OR streptovaricin OR sulbactam OR sulbenicillin OR talampicillin OR teicoplanin OR tetracycline OR thiamphenicol OR thiostrepton OR ticarcillin OR tobramycin OR troleandomycin OR tylosin OR tyrocidine OR tyrothricin OR valinomycin OR vancomycin OR vernamycin* OR viomycin* OR virginiamycin* OR "beta-lactam" OR "beta-lactams") AND db: ("LILACS") AND type˙of˙study:("clinical˙trials")

Appendix 4. Previous search strategy

In this updated review, we searched the Cochrane Central Register of Controlled trials (CENTRAL) (*The Cochrane Library* 2007, issue 4), which includes the Acute Respiratory Infections (ARI) Group's Specialised Register; MEDLINE (1966 to December 2007); and EMBASE (1974 to December 2007). For details of the search strategy used, see Appendix 2.
The updated MEDLINE (OVID) search used the following search strategy:
1 RANDOMIZED CONTROLLED TRIAL.pt. (228029)
2 CONTROLLED CLINICAL TRIAL.pt. (73939)
3 RANDOMIZED CONTROLLED TRIALS.sh. (46488)
4 RANDOM ALLOCATION.sh. (56676)
5 DOUBLE BLIND METHOD.sh. (89072)
6 SINGLE-BLIND METHOD.sh. (10505)
7 or/1-6 (387195)
8 HUMANs.sh. (9533289)
9 ANIMALs.sh. (3970623)
10 9 not 8 (3018353)
11 7 not 10 (364156)
12 CLINICAL TRIAL.pt. (431113)
13 exp Clinical Trials/ (185629)
14 (clin$ adj25 trial$).ti,ab. (124831)
15 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab. (88283)
16 PLACEBOS.sh. (25705)
17 placebo$.ti,ab. (99261)
18 random$.ti,ab. (357426)
19 or/12-18 (787581)
20 19 not 10 (731504)
21 11 or 20 (748271)
22 exp BRONCHITIS/ (22484)
23 acute bronchit$.mp. [mp=title, original title, abstract, name of substance word, subject heading word] (884)
24 exp Respiratory Tract Infections/ (215767)
25 or/22-24 (217540)
26 Anti-Bacterial Agents/ (157181)
27 exp Lactams/ (90537)
28 exp Tetracyclines/ (31342)
29 exp Aminoglycosides/ (97899)
30 exp Glycopeptides/ (37656)
31 exp Macrolides/ (66142)
32 antibiotic$.mp. [mp=title, original title, abstract, name of substance word, subject heading word] (166066)
33 exp alamethicin/ or exp amdinocillin/ or exp amdinocillin pivoxil/ or exp amikacin/ or exp amoxicillin/ or exp amoxicillin-potassium clavulanate combination/ or exp ampicillin/ or exp aurodox/ or exp azithromycin/ or exp azlocillin/ or exp aztreonam/ or exp bacitracin/ or exp bacteriocins/ or exp brefeldin a/ or exp butirosin sulfate/ or exp candicidin/ or exp carbenicillin/ or exp carfecillin/ or exp cefaclor/

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

or exp cefadroxil/ or exp cefamandole/ or exp cefazolin/ or exp cefixime/ or exp cefmenoxime/ or exp cefmetazole/ or exp cefonicid/ or exp cefoperazone/ or exp cefotaxime/ or exp cefotetan/ or exp cefotiam/ or exp cefoxitin/ or exp cefsulodin/ or exp ceftazidime/ or exp ceftizoxime/ or exp ceftriaxone/ or exp cefuroxime/ or exp cephacetrile/ or exp cephalexin/ or exp cephaloglycin/ or exp cephaloridine/ or exp cephalosporins/ or exp cephalothin/ or exp cephapirin/ or exp cephradine/ or exp chloramphenicol/ or exp chlortetracycline/ or exp citrinin/ or exp clarithromycin/ or exp clavulanic acid/ or exp clavulanic acids/ or exp clindamycin/ or exp cloxacillin/ or exp colistin/ or exp cyclacillin/ or exp dactinomycin/ or exp daptomycin/ or exp demeclocycline/ or exp dibekacin/ or exp dicloxacillin/ or exp dihydrostreptomycin sulfate/ or exp distamycins/ or exp doxycycline/ or exp echinomycin/ or exp edeine/ or exp erythromycin/ or exp erythromycin estolate/ or exp erythromycin ethylsuccinate/ or exp floxacillin/ or exp framycetin/ or exp fusidic acid/ or exp gentamicins/ or exp gramicidin/ or exp imipenem/ or exp lactams/ or exp lasalocid/ or exp leucomycins/ or exp lymecycline/ or exp mepartricin/ or exp methacycline/ or exp methicillin/ or exp mezlocillin/ or exp mikamycin/ or exp minocycline/ or exp miocamycin/ or exp moxalactam/ or exp mupirocin/ or exp mycobacillin/ or exp nafcillin/ or exp nebramycin/ or exp nigericin/ or exp nisin/ or exp novobiocin/ or exp nystatin/ or exp ofloxacin/ or exp oligomycins/ or exp oxacillin/ or exp oxytetracycline/ or exp penicillanic acid/ or exp penicillic acid/ or exp penicillin g/ or exp penicillin g, benzathine/ or exp penicillin g, procaine/ or exp penicillin v/ or exp piperacillin/ or exp pivampicillin/ or exp polymyxin b/ or exp polymyxins/ or exp pristinamycin/ or exp prodigiosin/ or exp rifabutin/ or exp ristocetin/ or exp rolitetracycline/ or exp roxarsone/ or exp rutamycin/ or exp sirolimus/ or exp sisomicin/ or exp spectinomycin/ or exp streptogramin a/ or exp streptogramin group a/ or exp streptogramin group b/ or exp streptogramins/ or exp streptovaricin/ or exp sulbactam/ or exp sulbenicillin/ or exp talampicillin/ or exp teicoplanin/ or exp tetracycline/ or exp thiamphenicol/ or exp thiostrepton/ or exp ticarcillin/ or exp tobramycin/ or exp troleandomycin/ or exp tylosin/ or exp tyrocidine/ or exp tyrothricin/ or exp valinomycin/ or exp vancomycin/ or exp vernamycin b/ or exp viomycin/ or exp virginiamycin/ or exp beta-lactams/ (211481)
34 or/26-33 (499372)
35 21 and 25 and 34 (4684)
36 limit 35 to ed=20040103-20070201 (761)
37 from 36 keep 1-761 (761)

FEEDBACK

Data reported on adverse effects

Summary

We would like to draw attention to the misleading statement of authors conclusions for this review. The authors conclusion in the abstract reads: "Overall, antibiotics appear to have a modest beneficial effect in patients who are diagnosed with acute bronchitis. THE MAGNITUDE OF THIS BENEFIT, HOWEVER, IS SIMILAR TO THAT OF THE DETRIMENT FROM POTENTIAL ADVERSE EFFECTS."
The data reported on adverse effects does not seem to support this conclusion.
Graph 07 showing the number of participants with adverse effects in the antibiotics and control groups illustrates that adverse events in the antibiotics group reach significance in just one small study (King 1996), and the non-significant pooled estimate is clearly stated in the results section: "The overall relative risk (RR) of adverse effects was 1.22 (95% CI 0.94 to 1.58)."
We would like to recommend that the authors amend their conclusions to take account of these comments.
Submitter agrees with default conflict of interest statement: I certify that I have no affiliations with or involvement in any organisation or entity with a financial interest in the subject matter of my feedback.

Reply

We accept that our conclusions are overly pessimistic about side effects from antibiotic therapy. The pooled results from the updated review changed after inclusion of an additional RCT (Matthys 2000, see Figure 8 of the review), making adverse events less likely. We acknowledge that we did not change the tone of our conclusions to reflect this greater uncertainty concerning side effects.
We have amended the conclusion in the abstract to reflect the updated results concerning side effects to the following sentence:
"The magnitude of this benefit, however, needs to be considered in the broader context of potential side effects, medicalisation for a self-limiting condition, increased resistance to respiratory pathogens and cost of antibiotic treatment."

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Tom Fahey
Lorne Becker
John Smucny
Rick Glazier

Contributors

Paul Garner and Helen Smith
Feedback added 21 May 2005

Correction to updated review

Summary

Dear Authors,
Compared to the version published in the Cochrane Database of Systematic Reviews 2002, issue 2, the current version of the review included two more studies (Matthys, 2000; Evans, 2003). By consequence, some comparisons (02, 04-07) were updated. Therefore, the abstract should start with "Eleven studies involving over 1250 patients" instead of "Nine trials involving over 750". But, more importantly, except for comparison 07: Adverse effects, the values of the comparisons already mentioned in the abstract still need to be adjusted, i.e. 05: Not improved by physician's global assessment at follow-up visit (RR 0.44; 95% CI 0.30,0.65; NNT 10; 95% CI ...) instead of (RR 0.52; 95% CI 0.31,0.85; NNT 14; 95% CI 8 to 50);06: Abnormal lung exam at follow-up visit (RR 0.54; 95% CI 0.41,0.70; NNT 6; 95% CI ...) instead of (RR 0.48; 95% CI 0.26,0.89; NNT 11; 95% CI 6 to 50); Finally, due to the inclusion of (Matthys, 2000) comparison 02: Night cough at follow-up visit, now shows a significant difference between antibiotics and placebo(RR 0.67; 95% CI 0.54,0.83; NNT 7 ; 95% CI ...) instead of (RR 0.76; 95% CI 0.45,1.30). This comparison should thus be removed from the statement starting with "There were nog significant differences regarding the presence of night cough, productive cough, ..." and added to the previous sentence showing the benefits of antibiotic treatment. Given the difficulties in distinguishing upper from lower respiratory tract infections in daily practice and given the results of the study by Little et al. mentioned as ongoing study, the conclusions are still justified.
With kind regards.
Submitter agrees with default conflict of interest statement:I certify that I have no affiliations with or involvement in any organisation or entity with a financial interest in the subject matter of my feedback.

Reply

Thank you for your comments regarding inconsistencies noted in the previous update of the review. The review has been updated again over the last nine months and these inconsistencies were noted and corrected. The Little study has since been published and is now incorporated in this new version of the review.
Susan Smith
Tom Fahey
John Smucny
Lorne Becker

Contributors

Samuel Coenen
(Feedback added 01 May 2008)

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

WHAT'S NEW

Last assessed as up-to-date: 15 January 2014.

Date	Event	Description
15 February 2014	New citation required but conclusions have not changed	Review updated and strengthens the conclusion suggesting no evidence to support use of antibiotics in patients with acute bronchitis. The analysis of adverse effects has been updated by the addition of data from the largest study conducted to date and now indicates a statistically significant rate of adverse effects in the antibiotic treated groups
15 January 2014	New search has been performed	Searches were updated and one of the ongoing trials has been published and is now included in the review (Llor 2013). We identified one new included study (Little 2013).

HISTORY

Protocol first published: Issue 1, 1996

Review first published: Issue 1, 1997

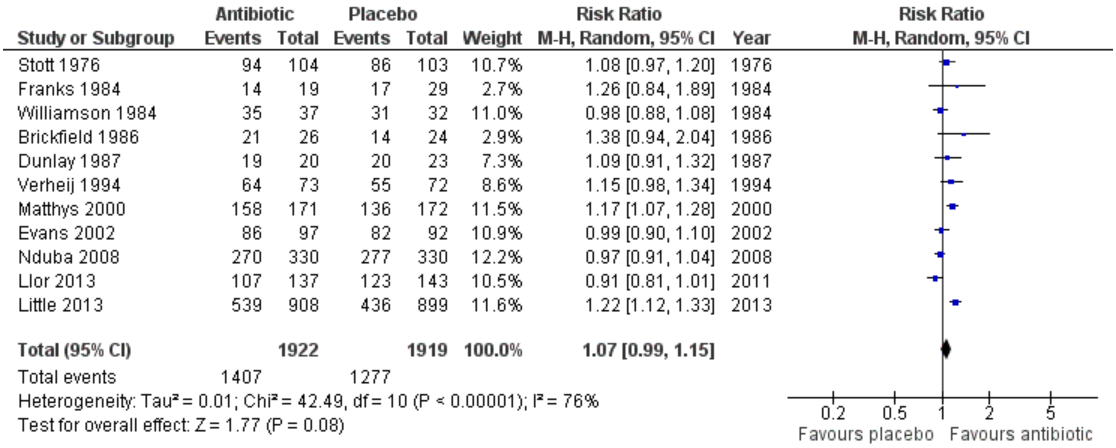
Date	Event	Description
1 March 2012	Amended	Correction made to Analysis 6.1 'Clinically improved' (Figure 1) as error noted in data entry relating to Stott 1976. This does not change the specific conclusions for this analysis or the overall conclusions of the review.
6 September 2010	New search has been performed	Searches updated and one new trial was included (Nduba 2008). The conclusions remain unchanged.
5 August 2010	Amended	Contact details updated
30 April 2008	Feedback has been incorporated	Feedback and response added
18 December 2007	New search has been performed	Searches conducted
11 December 2007	Amended	Converted to new review format
22 May 2005	Amended	Conclusions changed in the abstract
21 May 2005	Feedback has been incorporated	Feedback and response added
25 March 2004	New search has been performed	Searches conducted

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

(*Continued*)

29 February 2000	New search has been performed	Updated search Issue 4, 2000. No additional trials found, but were able to obtain unpublished data from three trials that were not included in the original review. The trials were not included in the first review because the participants in the trials as a whole did not meet our inclusion criteria. However, the trials each contained a subgroup of patients that did meet our inclusion criteria. We were also able to obtain additional unpublished data from some of the trials that were originally included
27 August 1997	New search has been performed	Review first published Issue 4, 1997

Figure 1. Forest plot of comparison: Clinically improved, outcome: number of patients reporting no limitations or described as cured/well/symptoms resolved or globally improved.



Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

CONTRIBUTIONS OF AUTHORS

Lorne Becker (LB) conceived, co-ordinated, and designed the original review; screened the search results for acceptable trials; entered and analyzed data; wrote the initial draft of the review; incorporated feedback from the other authors into the final draft; and participated in the updating the review in 2004 and 2009.

John Smucny (JS) screened the search results for acceptable trials; graded and extracted data from trials; entered and analyzed data; interpreted data independently, and then as a group; updated the search and independently re-extracted data; co-wrote the 2004 and 2009 update.

Tom Fahey (TF) joined the team for the 2000 update and helped co-ordinate the review with JS; updated the search and independently re-extracted data; provided unpublished data from a number of the studies; interpreted data independently, and then as a group; co-wrote the 2004 update; helped co-ordinate the 2009 update; independently assessed potentially eligible studies; and co-wrote the 2009 update.

Susan Smith (SS) joined the team for the 2009, 2011 and 2013 updates and helped co-ordinate the updates with TF; updated the search; independently assessed potentially eligible studies; and was the lead author for the 2009, 2011 and 2013 updates.

DECLARATIONS OF INTEREST

The authors have no conflict of interest in relation to this review.

SOURCES OF SUPPORT

Internal sources

- Center for Evidence-Based Practice, State University of New York, Upstate Medical University, Syracuse, New York, USA.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Anti-Bacterial Agents [*therapeutic use]; Bronchitis [*drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Humans

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.