

Over-the-counter (OTC) medications to reduce cough as an adjunct to antibiotics for acute pneumonia in children and adults (Review)

Chang CC, Cheng AC, Chang AB



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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
SUMMARY OF FINDINGS FOR THE MAIN COMPARISON	3
BACKGROUND	5
OBJECTIVES	5
METHODS	5
RESULTS	8
Figure 1.	9
Figure 2.	10
DISCUSSION	12
AUTHORS' CONCLUSIONS	13
ACKNOWLEDGEMENTS	13
REFERENCES	13
CHARACTERISTICS OF STUDIES	15
DATA AND ANALYSES	24
Analysis 1.1. Comparison 1 Children - global assessment, Outcome 1 Not cured or not improved.	25
Analysis 1.2. Comparison 1 Children - global assessment, Outcome 2 Not improved.	25
Analysis 1.3. Comparison 1 Children - global assessment, Outcome 3 Not cured.	26
Analysis 2.1. Comparison 2 Children - cough score, Outcome 1 Mean cough score at day 3.	26
Analysis 2.2. Comparison 2 Children - cough score, Outcome 2 Mean score at day 10.	27
Analysis 3.1. Comparison 3 Adults - global assessment, Outcome 1 Not cured or not improved.	27
Analysis 3.2. Comparison 3 Adults - global assessment, Outcome 2 Not improved.	28
Analysis 3.3. Comparison 3 Adults - global assessment, Outcome 3 Not cured.	28
Analysis 4.1. Comparison 4 Combined children and adults, Outcome 1 Not cured or not improved.	29
Analysis 4.2. Comparison 4 Combined children and adults, Outcome 2 Not improved.	29
Analysis 4.3. Comparison 4 Combined children and adults, Outcome 3 Not cured.	30
APPENDICES	30
WHAT'S NEW	33
HISTORY	33
CONTRIBUTIONS OF AUTHORS	34
DECLARATIONS OF INTEREST	34
SOURCES OF SUPPORT	34
INDEX TERMS	34

[Intervention Review]

Over-the-counter (OTC) medications to reduce cough as an adjunct to antibiotics for acute pneumonia in children and adults

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ABSTRACT

Background

Cough is often distressing for patients with pneumonia. Accordingly they often use over-the-counter (OTC) cough medications (mucolytics or cough suppressants). These might provide relief in reducing cough severity, but suppression of the cough mechanism might impede airway clearance and cause harm.

Objectives

To evaluate the efficacy of OTC cough medications as an adjunct to antibiotics in children and adults with pneumonia.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2011, Issue 3) which contains the Acute Respiratory Infections Group's Specialised Register, MEDLINE (January 1966 to July week 4, 2011), OLDMEDLINE (1950 to 1965), EMBASE (1980 to August 2011), CINAHL (2009 to August 2011), LILACS (2009 to August 2011) and Web of Science (2009 to August 2011).

Selection criteria

Randomised controlled trials (RCTs) in children and adults comparing any type of OTC cough medication with placebo, or control medication, with cough as an outcome and where the cough is secondary to acute pneumonia.

Data collection and analysis

We independently selected trials for inclusion. We extracted data from these studies, assessed them for methodological quality without disagreement and analyzed using standard methods.

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Main results

Four studies with a total of 224 participants were included; one was performed exclusively in children and three in adolescents or adults. One using an antitussive had no extractable pneumonia-specific data. Three different mucolytics (bromhexine, ambroxol, neltexine) were used in the remaining studies, of which only two had extractable data. They demonstrated no significant difference for the primary outcome of 'not cured or not improved' for mucolytics. A secondary outcome of 'not cured' was reduced (odds ratio (OR) for children 0.36, 95% confidence interval (CI) 0.16 to 0.77; number needed to treat to benefit (NNTB) at day 10 = 5 (95% CI 3 to 16) and OR 0.32 for adults (95% CI 0.13 to 0.75); NNTB at day 10 = 5 (95% CI 3 to 19). In a post hoc analysis combining data for children and adults, again there was no difference in the primary outcome of 'not cured or not improved' (OR 0.85, 95% CI 0.40 to 1.80) although mucolytics reduced the secondary outcome 'not cured' (OR 0.34, 95% CI 0.19 to 0.60; NNTB 4, 95% CI 3 to 8).

Authors' conclusions

There is insufficient evidence to decide whether OTC medications for cough associated with acute pneumonia are beneficial. Mucolytics may be beneficial but there is insufficient evidence to recommend them as an adjunctive treatment for acute pneumonia. This leaves only theoretical recommendations that OTC medications containing codeine and antihistamines should not be used in young children.

PLAIN LANGUAGE SUMMARY

Over-the-counter medications to help reduce cough for children and adults on antibiotics for acute pneumonia

There are many causes of acute cough, one of which is pneumonia. Cough is burdensome and impairs quality of life. To ameliorate cough, over-the-counter (OTC) medications are commonly used by patients and recommended by healthcare staff as adjuncts in the treatment of pneumonia. There are many classes of OTCs for cough, such as mucolytics (medications that can reduce the thickness of mucus) and antitussives (medications that suppresses cough).

In this review we found four studies with a total of 224 participants that were suitable for inclusion; one was performed exclusively in children and three in adolescents or adults. However, data could only be obtained from two studies; both studies used mucolytics (ambroxol and bromhexine) in conjunction with antibiotics. Combining these two studies, the rate of cure or improvement in cough of people who received mucolytics was similar to those who did not. However, in the secondary analysis, children who received a mucolytic were more likely to be cured of cough (number needed to treat to benefit (NNTB) at day 10 was 5 (95% CI 3 to 16) for children and 4 (95% CI 3 to 8) for adults). There were no reported increased adverse events in the treatment group.

The range of possible adverse events in OTCs for cough is wide and includes minimal adverse events (such as use of honey) to serious adverse events such as altered heart rate patterns, drowsiness and death in young children. The studies included in this review did not report any detectable increase in adverse events.

The review has substantial limitations due to the unavailability of data from studies. Also there are no studies that have used other common OTCs used for cough, such as antihistamines and antitussives.

Thus, there is insufficient evidence to draw any conclusions about whether OTC medications taken as an adjunctive treatment for cough associated with acute pneumonia are beneficial or not. Mucolytics may be beneficial but the lack of consistent evidence precludes recommending the routine use of mucolytics as an adjunct in the treatment of troublesome cough associated with pneumonia in children or adults.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Mucolytics as an adjunct to antibiotics to reduce cough in acute pneumonia in children and adults						
Patient or population: children and adults with acute pneumonia Settings: any Intervention: mucolytics (and antibiotics) ¹ Comparison: antibiotics only						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Antibiotics only	Mucolytics (and antibiotics)				
Cough score Scale from: 0 (absent) to 3 (very severe) (follow-up: 3 days)	The mean cough score in the control groups was 1.45	The mean cough score in the intervention groups was 0.25 lower (0.33 to 0.17 lower)		120 (1)	⊕⊕○○ low ^{2,3,4}	Data for children only
Number of people who had not improved or had not been cured (follow-up: 7 to 10 days)	16 per 100	14 per 100 (7 to 26)	OR 0.85 (0.4 to 1.8)	221 (2)	⊕⊕○○ low ^{2,5}	Fewer people represents a benefit
Adverse events (follow-up: 10 days)	See comment	See comment	Not estimable	120 (1)	See comment	1 study in children provided data specific to participants with pneumonia - there were no adverse events
Complications (e.g. medication change)	See comment	See comment	Not estimable	0 (0)	See comment	Complications were not measured in the trials

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; OR: odds ratio.

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

- ¹ In addition to antibiotics, people with pneumonia often use over-the-counter (OTC) cough medications when at home or request OTC cough medications when in hospital to suppress an annoying cough. There is a question as to whether suppressing cough may prolong pneumonia. Over-the-counter cough medications can include antitussives, expectorants, antihistamine-decongestants, antihistamines and mucolytics (such as bromhexine, ambroxol and neltexine).
- ² Allocation concealment unclear.
- ³ Scale not validated.
- ⁴ Sparse data.
- ⁵ Sparse data; confidence interval does not rule out the potential for 'more people' not improved or cured with mucolytics.

BACKGROUND

Description of the condition

Cough is the most common symptom presenting to general practitioners (Britt 2002; Cherry 2003). Acute cough (duration less than two weeks) (Chang 2006) has multiple causes, including pneumonia. Whatever the cause, attempting to reduce the impact of the symptom of cough is reflected in the billions spent on over-the-counter (OTC) cough medications. Cough impairs quality of life (French 2002) and causes significant anxiety to the parents of children (Cornford 1993). Accordingly, patients with pneumonia sometimes self medicate with OTC cough medications in ambulatory settings, or ask for them in hospital.

Description of the intervention

A Cochrane review showed that antihistamine alone has little clinical benefit in adults or children for the common cold, although in combination they might be of (non-significant) benefit (De Sutter 2003). In the management of acute cough, in the ambulatory setting, combination rather than single OTC drugs showed a benefit (Smith 2009). Of the few data available in young children, antihistamines, neither singly nor in combination, were effective for relieving acute cough (De Sutter 2003; Smith 2009). Moreover, they are associated with potentially significant adverse events including altered consciousness, arrhythmia and death (Gunn 2001; Kelly 2004). None of these reviews included patients with pneumonia (De Sutter 2003; Smith 2009). There are also Cochrane reviews on chronic non-specific cough, however this is unrelated to this review which focuses on acute cough associated with pneumonia.

How the intervention might work

Cough is usually divided into acute or chronic according to its duration and age group. It is defined as chronic if over eight weeks duration in adults, and over three to four weeks in children (Chang 2005). This reflects the different conditions causing chronic cough in different age groups. In contrast, in this review we examined the efficacy of OTC medication for acute cough in acute pneumonia, where the pathophysiological processes (albeit poorly understood) are likely to be the same in children and adults. Methods for determining cough outcomes are similar in adults and children, although these methods remain poorly standardised. Objective measurements of cough include cough frequency and cough sensitivity outcomes, whilst subjective measurements of cough may broadly encompass quality of life and outcomes based on diaries etc. (Birring 2006; Chang 2003).

Why it is important to do this review

Although OTC cough medications might provide some relief by reducing the severity of the cough, they might also be harmful in prolonging pneumonia (by suppressing the cough reflex, which might cause retention of airway debris). Thus, a systematic review of their benefits or harms is useful to help guide clinical practice.

OBJECTIVES

To evaluate the efficacy of OTC medications for cough as an adjunct to antibiotics in children and adults with pneumonia.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) comparing any type of OTC cough medication with a placebo (or control group) with cough as an outcome and where cough is secondary to acute pneumonia. We excluded quasi-randomised trials.

Types of participants

We considered studies of both children and adults with cough of less than four weeks in duration that was related to pneumonia. We specifically excluded studies of cough of more than four weeks in duration and cough related to another underlying cardio-respiratory condition (for example, suppurative lung disease, chronic obstructive airway disease, asthma). However, we considered studies which included cough of mixed aetiologies if data were available for the subgroup of patients with pneumonia.

Types of interventions

RCT comparisons of any type of OTC cough medication as an adjunct therapy to antibiotics. We did not include trials comparing only two or more medications without a placebo comparison group. We included trials that included the use of other medications or interventions if all participants had equal access to such medications (including antibiotics) or interventions.

Types of outcome measures

We attempted to obtain data on at least one of the following outcome measures.

Primary outcomes

1. Proportions of participants who were not cured or not substantially improved at follow-up (failure to improve was measured according to the hierarchy listed below in [Secondary outcomes](#)).

Secondary outcomes

1. Proportions of participants who were not cured at follow-up.
2. Change in quantitative differences in cough (cough frequency, cough scores, other quantitative outcomes based on cough diary).
3. Proportions experiencing adverse effects of the intervention (for example, sleepiness, nausea, etc.).
4. Proportions experiencing complications (for example, requirement for medication change, etc.).

We adopted and recorded individual trial definitions.

As it was likely that studies may have differed in their definitions of cure and improvement, we adopted a hierarchical approach that employed the reported outcome measures. For example, if both an objective measure and a subjective measure of cough frequency were reported, we were to adopt the objective measure in assessing the efficacy of treatment. Our hierarchy of outcome measures was as follows.

1. Objective measurements of cough indices (cough frequency, cough receptor sensitivity).
2. Symptomatic (quality of life, Likert scale, visual analogue scale, level of interference of cough, outcomes-based cough diary): assessed by the patient (adult or child).
3. Symptomatic (quality of life, Likert scale, visual analogue scale, level of interference of cough, outcomes-based cough diary): assessed by the parents or carers.
4. Symptomatic (Likert scale, visual analogue scale, level of interference of cough, outcomes-based cough diary): assessed by clinicians.
5. Fever, respiratory rate, oxygen requirement.
6. Non-clinical outcomes (chest radiology, white cell count, C-reactive protein, erythrocyte sedimentation rate, lung function test (spirometry)).
7. Eradication of micro-organism(s) causing the pneumonia.

Search methods for identification of studies

Electronic searches

For this update we searched the Cochrane Central Register of Controlled Trials (CENTRAL) 2011, Issue 3, part of *The Cochrane Library*, www.thecochranelibrary.com (accessed 8 August 2011), which contains the Acute Respiratory Infections Group's Specialised Register, MEDLINE (January 1966 to July week 4, 2011),

OLDMEDLINE (1950 to 1965), EMBASE (1980 to August 2011), CINAHL (2009 to August 2011), LILACS (2009 to August 2011) and Web of Science (2009 to August 2011).

We used the following search strategy to search MEDLINE and CENTRAL. We adapted the search strategy for EMBASE (see [Appendix 2](#)), CINAHL (see [Appendix 3](#)), LILACS (see [Appendix 4](#)) and Web of Science (see [Appendix 5](#)).

MEDLINE (OVID)

```
1 Cough/ (10608)
2 cough*.tw. (28391)
3 1 or 2 (31582)
4 exp Pneumonia/ (65782)
5 (pneumon* or bronchopneumon*).tw. (113126)
6 4 or 5 (138604)
7 3 and 6 (4162)
8 exp Antitussive Agents/ (18518)
9 antitussiv*.tw,nm. (2689)
10 exp Expectorants/ (11882)
11 expectorant*.tw,nm. (2292)
12 exp Cholinergic Antagonists/ (70293)
13 (cholinergic adj2 (blocking or antagonist*)).tw,nm. (4262)
14 (anticholinergic* or anti-cholinergic*).tw,nm. (8857)
15 exp Histamine H1 Antagonists/ (30616)
16 histamine h1 antagonist*.tw,nm. (14125)
17 (antihistamin* or anti-histamin*).tw,nm. (10001)
18 mucolytic*.tw,nm. (1072)
19 exp Drug Combinations/ (53453)
20 drug combination*.tw. (6928)
21 exp Nonprescription Drugs/ (4455)
22 ((non prescribed or non-prescribed or nonprescribed or non prescription* or non-prescription* or nonprescription*) adj3 (drug* or medicin* or pharmaceut* or medicat*)).tw. (842)
23 (over-the-counter* or over the counter or otc).tw. (6246)
24 (cough* adj3 (mixture* or suppress* or medicin* or remed* or relief* or formula* or syrup*)).tw. (801)
25 or/8-24 (203333)
26 7 and 25 (120)
There were no language or publication restrictions.
```

Searching other resources

We also searched lists of references in relevant publications.

Data collection and analysis

Selection of studies

Two review authors (CCC, ABC) independently reviewed the literature searches to identify potentially relevant trials for full review from the title, abstract or descriptors. We conducted searches of bibliographies and texts to identify additional studies. The same

two review authors independently selected trials for inclusion from the full text, using specific criteria. There was no disagreement. A third review author (ACC) was the nominated adjudicator in case of any disagreements.

Data extraction and management

We reviewed trials that satisfied the inclusion criteria and extracted the following information: study setting; year of study; source of funding; patient recruitment details (including number of eligible patients); inclusion and exclusion criteria; other symptoms; randomization and allocation concealment method; numbers of participants randomized; blinding (masking) of participants, care providers and outcome assessors; dose and type of intervention; duration of therapy; co-interventions; numbers of patients not followed up; reasons for withdrawals from study protocol (clinical, side effects, refusal and other); details on side effects of therapy and whether intention-to-treat (ITT) analyses were possible. We extracted data on the outcomes described previously. It was planned that further information would be requested from the trial authors, where required.

Assessment of risk of bias in included studies

Two review authors (CCC, ABC) independently performed a potential bias assessment on studies included in the previous review. We described seven components of potential biases under [Assessment of reporting biases](#) in our updated review

Measures of treatment effect

We undertook an initial qualitative comparison of all the individually analyzed studies to determine if pooling of results (meta-analysis) was reasonable. This took into account differences in study populations, inclusion and exclusion criteria, interventions, outcome assessment and estimated effect size. We included the results from studies that met the inclusion criteria and reported any of the outcomes of interest in the subsequent meta-analyses.

We calculated individual and pooled statistics for continuous outcomes measured on the same metrics as mean differences (MD) and standard mean differences, as indicated, with 95% confidence intervals (CIs). We combined data for continuous outcomes measured on different metrics, with a standardised mean difference (SMD). We calculated individual and pooled statistics as odds ratio (OR) with 95% CIs for dichotomous variables.

Unit of analysis issues

Had there been any cross-over studies, we would have calculated mean treatment differences from raw data, extracted or imputed and entered as fixed-effect generic inverse variance (GIV) outcomes, to provide summary weighted differences and 95% CIs. Only data from the first arm would have been included in a meta-

analysis where data were combined with parallel studies ([Elbourne 2002](#)).

Dealing with missing data

We planned to contact trial authors for missing data when the studies were less than 15 years old.

Assessment of heterogeneity

We described any heterogeneity between the study results and tested to see if it reached statistical significance, using the I^2 statistic ([Higgins 2003](#)). Heterogeneity is considered significant when the P value of the Chi^2 test is < 0.10 ([Higgins 2011](#)). We would have included the 95% CI estimate using a random-effects model had there been concerns about statistical heterogeneity.

Assessment of reporting biases

In this updated review, in line with the new Cochrane process, we use the 'Risk of bias' tool to assess methodological quality according to: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) and other possible bias. In our previous reviews we assessed bias in accordance with a different scale but we were asked to remove this in the current update.

While there are other possible biases (such as publication bias detected by funnel plot) as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)), these were not included.

Data synthesis

We calculated odds ratios (ORs) using a modified ITT analysis for dichotomous outcome variables of each individual study. This analysis assumed that participants not available for outcome assessment had not improved (and probably represented a conservative estimate of effect). We calculated the summary weighted ORs and 95% CI (fixed-effect model) using the computer program [RevMan 2011](#). We calculated the number needed to treat to benefit (NNTB) from the pooled OR and its 95% CI, applied to a specified baseline risk using an online calculator ([Cates 2003](#)). We assumed the cough indices to be normally distributed continuous variables so that the mean difference in outcomes could be estimated (mean difference). We would have estimated the standardised mean difference if studies had reported outcomes using different measurement scales.

Subgroup analysis and investigation of heterogeneity

We planned an a priori subgroup analysis for:

1. children (14 years and younger) versus adolescents and adults (older than 14 years);
2. hospitalised versus ambulatory settings;
3. classes of OTC cough medications:
 - i) antitussives (codeine and derivatives);
 - ii) expectorants;
 - iii) mucolytics;
 - iv) antihistamine-decongestant combinations;
 - v) antihistamines alone;
 - vi) other drug combinations;
 - vii) males versus females in adults.

Sensitivity analysis

It was planned that sensitivity analyses be carried out to assess the impact of potentially important factors on the overall outcomes:

1. study quality;
2. study size;
3. variation in the inclusion criteria;
4. differences in the medications used in the intervention and comparison groups;
5. differences in outcome measures;
6. analysis using random-effects model;
7. analysis by 'treatment received';
8. analysis by 'ITT';
9. analysis by study design, parallel and cross-over studies.

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#).

Results of the search

In the first version of this review ([Chang 2007](#)), the search identified 238 potentially relevant titles. After reviewing the abstracts, we obtained 21 full-text papers; we excluded 17 (details are provided in the [Characteristics of excluded studies](#) table), most on the basis of being non-randomised, with no placebo. A review article ([Ida 1997](#)) described three studies of dimemorfan (a dextromethorphan analogue), which were not found by the search. One of these was described as a placebo-controlled trial (the other two were not), but we could not obtain it, and nor were sufficient details provided in the review article ([Ida 1997](#)). Another paper described three studies, of which one appeared to include patients with acute lower respiratory tract infection (specified as acute bronchitis or bronchoalveolitis but which may have included patients with pneumonia) ([Mancini 1996](#)). We attempted to contact the

trial authors but were not able to extract data on the subgroup of patients with pneumonia, and thus we excluded the trial from further analysis.

In the 2009 update ([Chang 2010](#)), we identified two studies on erdosteine (a mucolytic agent) but these were excluded as they are available only on medical prescription in countries with tight regulatory control of medications such as USA, Australia and the UK ([Balli 2007](#); [Titti 2000](#)). In this 2011 update, we identified 32 potential studies but none fulfilled the inclusion criteria.

Included studies

Four studies were included, as described in the [Characteristics of included studies](#) table; all were available in English. However, data specific for pneumonia were only available in two papers ([Principi 1986](#); [Roa 1995](#)). Authors of three papers did not respond to our correspondence requesting for further pneumonia-specific data.

Of the included studies, one study was exclusively in children ([Principi 1986](#)), two were exclusively in adults ([Aquilina 2001](#); [Azzopardi 1964](#)) and one included adolescents and adults ([Roa 1995](#)). One study utilised an antitussive (Dimyrlil) ([Azzopardi 1964](#)) and three of the studies examined the efficacy of different formulations of mucolytics (bromhexine ([Roa 1995](#)), neltexine ([Aquilina 2001](#)) and ambroxol ([Principi 1986](#))). In two of these studies, the concomitant antibiotics used were reported ([Principi 1986](#); [Roa 1995](#)). Two studies were multi-centre studies ([Principi 1986](#); [Roa 1995](#)) of which the funding was unspecified. Two studies were single-centre studies ([Aquilina 2001](#); [Azzopardi 1964](#)). One study was a controlled non-placebo study ([Roa 1995](#)) and the rest utilised a randomized placebo-controlled design ([Aquilina 2001](#); [Azzopardi 1964](#); [Principi 1986](#)). All but one study ([Azzopardi 1964](#)) used a parallel design. The inclusion and exclusion criteria (that is, including the definition of pneumonia) varied between the studies; only one study was exclusively in patients with pneumonia ([Principi 1986](#)). In [Roa 1995](#), bacterial pneumonia was defined as the presence of recent productive phlegm, fever or leucocytosis ($> 10,000 \text{ mm}^3$) and pulmonary infiltrates on radiographic examination. In [Principi 1986](#) inclusion required either a positive blood culture for a well-defined bacterium or a chest X-ray (CXR) showing lobar or sub lobar involvement together with raised inflammatory markers, erythrocyte sedimentation rate $\geq 30 \text{ mm/h}$ and reactive C protein $\geq 25 \mu\text{g/mL}$. The two smaller papers ([Aquilina 2001](#); [Azzopardi 1964](#)) which contributed rather fewer numbers to the analysis did not clearly define pneumonia.

The outcomes of the studies also varied and none utilised a validated scale for cough. The larger trials, [Roa](#) and [Principi](#), were performed and published 12 and 21 years ago, respectively, and so were not methodologically as robust as one would expect of current-day trials ([Principi 1986](#); [Roa 1995](#)). The [Roa 1995](#) trial evaluated clinical response, bacteriological response and each clinical symptom by a visual analogue scale. Both clinical and bacteriological responses had clearly defined definitions; they defined cure

as complete disappearance of pre-treatment signs and symptoms, improvement as an improvement on the visual analogue scale but less than cure. [Principi 1986](#) evaluated clinical and radiological signs and used absolute numbers and severity scores to evaluate clinical symptoms and signs, including cough. The [Aquilina 2001](#) trial used severity scores on pre-specified examination days and at the end of therapy, the investigator expressed an overall assessment of the therapeutic efficacy. The [Azzopardi 1964](#) trial was more obviously subjective in its evaluation.

As described above, we excluded 17 trials (details are provided in the [Characteristics of excluded studies](#) table), most on the basis of being non-randomised, with no placebo.

Excluded studies

Risk of bias in included studies

In previous reviews, the agreement between the review authors for the scores was good: weighted Kappa score for the quality assessment scale was 0.63. In the updated 2011 version we completed a 'Risk of bias' table (see [Figure 1](#); [Figure 2](#)).

Figure 1. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

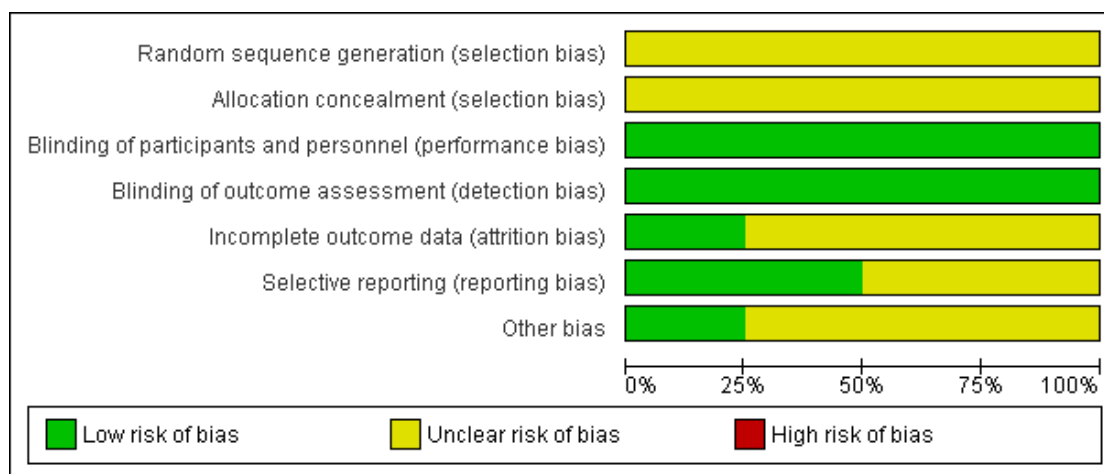


Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Aquilina 2001	?	?	+	+	?	?	?
Azzopardi 1964	?	?	+	+	?	?	?
Principi 1986	?	?	+	+	+	+	?
Roa 1995	?	?	+	+	?	+	+

Allocation

See 'Characteristics of included studies' table.

Blinding

See 'Characteristics of included studies' table.

Incomplete outcome data

See 'Characteristics of included studies' table.

Selective reporting

Limited reporting in studies. See 'Characteristics of included studies' table.

Other potential sources of bias

Nil known.

Effects of interventions

See: [Summary of findings for the main comparison](#)

In one study ([Azzopardi 1964](#)) the number of participants with pneumonia was not specified. In the other three included studies ([Aquilina 2001](#); [Principi 1986](#); [Roa 1995](#)) the total number of randomized participants was 555, of which 224 had pneumonia. The total number who completed the trials was 518, of which 219 had pneumonia. Given the lack of data, meta-analysis could not be performed on any outcome when children and adults were considered separately and, thus, sensitivity analysis was irrelevant. Single study results and the data and analysis section are described below.

Paediatric

Mucolytics

Principi reported that cough disappeared more rapidly in children treated with ambroxol than in the placebo group ([Principi 1986](#)). However, in the data and analysis section for the primary outcome of 'not cured or not improved' (defined on chest X-ray), there was no significant difference between groups (odds ratio (OR) 0.40, 95% confidence interval (CI) 0.10 to 1.62) ([Analysis 1.1](#)). There was also no difference between groups for the secondary outcome of 'no improvement' (OR 0.40, 95% CI 0.10 to 1.62) ([Analysis 1.2](#)). However, for the secondary outcome of clinically 'not cured' there was a significant difference between groups (defined on chest X-ray), as presented in the data and analysis section, favouring

the ambroxol group. The OR was 0.36 (95% CI 0.16 to 0.77) ([Analysis 1.3](#)) and the number needed to treat to benefit (NNTB) was 5 (95% CI 3 to 16).

For the outcome of cough scores Principi reported a significant difference between groups, favouring the ambroxol group from day three onwards ([Principi 1986](#)). The data and analysis section for mean cough scores on days 3 and 10 is shown in [Analysis 2.1](#) and [Analysis 2.2](#). For day 3, the mean difference was -0.25 (95% CI -0.33 to -0.17). For day 10, the mean difference was -0.15 (95% CI -0.17 to -0.13).

The trial authors reported no significant adverse events in either group ([Principi 1986](#)).

Other OTC cough medications

There were no studies on any other type of OTC medication for cough associated with pneumonia in children.

Adults

Antitussives

The Azzopardi study on 34 adults (total number assumed based on study design, see the [Characteristics of included studies](#) table) included adults with pneumonia (number unknown) in addition to other lower respiratory tract infection aetiologies ([Azzopardi 1964](#)). Data on those with pneumonia alone were not available and are not described here.

Mucolytics

The Roa study reported that for the total group (that is, adults with pneumonia and bronchitis) the differences between cough frequency on days three, five and seven and baseline were significantly larger in the bromhexine group compared to the control group ([Roa 1995](#)). There was also a difference between groups (favouring bromhexine) for cough discomfort and ease of expectoration on days three and five, but not on day seven, as well as sputum volume on day three, but not on days five or seven. There was no difference between the groups for difficulty in breathing or chest pain on any day. At final evaluation significantly more participants were 'cured' (46%) in the bromhexine group compared to the control group (34%) ([Roa 1995](#)).

Data specifically described for pneumonia were available only for global 'clinical response' and this is presented in the data and analysis section ([Analysis 3](#)). For the primary outcome of clinically 'not cured or not improved' there was no significant difference between groups (OR 1.21, 95% CI 0.48 to 3.04) ([Analysis 3.1](#)).

There was also no significant difference between groups for the secondary outcome 'not improved' (OR 1.21, 95% CI 0.48 to 3.04) (Analysis 3.2). However, like the results for children treated with a mucolytic, there was a significant difference between groups for the secondary outcome 'not cured' (OR 0.32, 95% CI 0.13 to 0.75), NNTB 5 (95% CI 3 to 19), favouring those on bromhexine (Analysis 3.3). The authors reported a total of 11 adverse events, six in the active treatment group and five in the control group (Roa 1995).

In the study using neltexine (a mucolytic), we could not obtain data specific for those with pneumonia (n = 3) (Aquilina 2001). The trial authors reported no significant adverse events in any of the groups (Aquilina 2001).

Other OTC cough medications

There were no studies on any other type of OTC medication for cough.

Combined data for children and adults

Mucolytics

In post hoc analysis, we combined data on children and adults. There was no significant statistical heterogeneity in any of the outcomes (Analysis 4.1 to Analysis 4.3). In the combined data, meta-analysis showed no significant difference between groups for the primary outcome of 'not cured or not improved' (OR 0.85, 95% CI 0.40 to 1.80) (Analysis 4.1). There was also no significant difference between groups for the secondary outcome 'not improved' (OR 0.80, 95% CI 0.38 to 1.67) (Analysis 4.2). However, Analysis 4.3 showed a significant difference between groups for the outcome 'not cured' (OR 0.34, 95% CI 0.19 to 0.60), NNTB 4 (95% CI 3 to 8), favouring those on a mucolytic.

Sensitivity analyses

The only appropriate sensitivity analysis that could be performed was that for Analysis 4 (combined children and adults). Statistical heterogeneity was absent but given the clinical heterogeneity we used a random-effects model to re-examine the results. This revealed that there was still no significant difference between groups for Analysis 4.1 ('not cured or not improved') but the OR was altered with a wider confidence interval (OR 0.79, 95% CI to 0.27 to 2.29). For Analysis 4.2 ('not improved'), the non-significant difference was also unaltered but the OR changed to 0.72 (95% CI 0.21 to 2.24). For Analysis 4.3 ('not cured'), the significant difference between groups was also preserved and there was no difference in the OR or 95% CI (OR 0.34, 95% CI 0.19 to 0.60), NNTB 4 (95% CI 3 to 8), favouring those on a mucolytic.

DISCUSSION

Only a few studies have examined over-the-counter (OTC) medications for cough related to pneumonia.

Summary of main results

Although four studies were included in this review, only data from two studies could be used (Principi 1986; Roa 1995). Both of these studies examined the efficacy of a mucolytic as an adjunct to the management of pneumonia and used cough as the principle outcome. In the primary outcome of 'not cured or not improved', there was no difference between groups when we considered children and adults separately, or when we combined data in a post hoc analysis. However, in one of the secondary outcomes ('not cured') the use of a mucolytic increased the cure rate similarly in both children and adults (number needed to treat to benefit (NNTB) = 5). Therefore, we cannot be confident of its efficacy. Nevertheless, based on Analysis 2.1, if a mucolytic is tried then the time to response (that is, the "expected timeframe to which a significant improvement is seen" (Chang 2006)), is three days. However, these data come from only a single study.

Overall completeness and applicability of evidence

OTC medications for cough consist of a variety of drugs used as sole agents or in combination. These drugs include antitussives (such as codeine derivatives), antihistamines and non-pharmaceutical medications (for example, menthol) (Eccles 2002). However, it is also possible that non-pharmaceutical additives used (such as sugar, alcohol) may have a therapeutic effect, such that the placebo effect of medications for cough has been reported to be as high as 85% (Eccles 2002). Thus, it is not surprising that although the total sample size for the combined studies was not small (N = 224), there was no effect seen for the primary outcome. Given that there was a significant difference between groups, further evaluation on mucolytics using more robust outcomes (as outlined in the 'Implications for research') is certainly warranted. Although adverse events were uncommon in the clinical trials identified in this study, there are case reports of severe adverse events, including severe morbidity and even death (Kelly 2004).

Quality of the evidence

The quality of the evidence is low as shown in the Summary of findings for the main comparison.

Potential biases in the review process

This systematic review is limited to four studies (with only two with extractable data) and in these studies only a single type of OTC medication for cough was examined. Thus, there is a clear lack of studies in this area. Also, the inclusion criteria and outcomes varied among trials.

Agreements and disagreements with other studies or reviews

A systematic review on adjunctive therapies for community-acquired pneumonia (CAP) reported “We found no clinical trials assessing the effectiveness of over-the-counter preparations for cough as an adjunct to antimicrobial treatment in patients with CAP” (Siempos 2008).

AUTHORS' CONCLUSIONS

Implications for practice

With the lack of evidence, the routine use of over-the-counter (OTC) cough medications in treating children or adults with troublesome cough associated with pneumonia cannot be recommended. Of those tested, mucolytics are the only type of OTC medication that has been shown to be possibly efficacious. The 'time to response' (subjective cough severity) is three days when used in adjunct to an appropriate antibiotic. In current practice it is recommended that young children are not given OTC cough

medications containing codeine derivatives and antihistamines because of the known adverse events of these medications.

Implications for research

Randomised controlled trials (RCTs) of OTC medications to determine their effectiveness in treating cough associated with pneumonia are clearly needed. Current guidelines advocate that studies of antitussives should take place in patients with a clearly defined clinical entity, such as pneumonia. Trials should be parallel studies and double-blinded, given the known problems in studying cough, specifically the large placebo and time period effects. Clinical, radiological and bacteriological responses should be objectively evaluated. Based on the above data, a short trial of seven days would suffice. Outcome measures for the clinical studies on cough should be clearly defined using validated subjective data and supported by objective data, if possible.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Aquilina 2001

Methods	Single-centre, double-blind, parallel, placebo-controlled RCT. Method of recruitment was not specified Concomitant antitussives, mucolytics and beta-2 agonist disallowed. Clinical evaluation performed on baseline, days 3, 7 and final. Participants assessed for signs and symptoms relevant to diagnosis of acute or chronic lung disease including sputum volume and characteristics, dyspnoea, cough, pulmonary auscultation, difficulty in expectorating Compliance not mentioned. Inclusion and exclusion criteria described in next column Description of withdrawals or drop-outs not mentioned
Participants	14 participants allocated to neltexine, 14 to placebo. Three within group had pneumonia but data specific to pneumonia were unavailable. Mean age of total group was 57.5 years (SD 3.04) Inclusion criteria: adults (aged > 18 years) with acute and chronic lung disease Exclusion criteria: pulmonary tuberculosis, lung cancer, allergy to neltexine, severe bronchospasm (requiring beta-2 agonist, corticosteroids or aminophylline), or pregnant or lactating women
Interventions	Neltexine (a mucolytic), 37.4 mg tds or placebo (1 tablet tds) for 10 to 12 days
Outcomes	Overall physicians' assessment of efficacy scored: excellent, good, moderate, not satisfactory. Exact quantification unspecified Sputum volume, sputum characteristics (1 = serous to 5 = very purulent), and 5-point scores for dyspnoea, cough, pulmonary auscultation, difficulty in expectorating, from 0 (absent) to 4 very severe
Notes	Wrote to authors with no response Data for pneumonia alone not available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo used
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Placebo used

Aquilina 2001 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Drop-outs unclear
Selective reporting (reporting bias)	Unclear risk	Data for pneumonia alone could not be extracted
Other bias	Unclear risk	Data for pneumonia alone could not be extracted. Single centre study, further information sought from trial authors with no response

Azzopardi 1964

Methods	Single-centre, double-blind, placebo-controlled RCT. Participants recruited from inpatients in the geriatric unit of Barnet General Hospital, England. The method of randomization and allocation was not described. When the medication (active or placebo) was considered ineffective, the pharmacist was asked to change to alternate treatment. Data card and observation record prepared for each participant, other medications recorded and authors indicated that these factors were taken into account when assessing response to trial drugs (but did not specify how). Inclusion and exclusion criteria not described. Description of withdrawals or drop-outs not mentioned	
Participants	Total randomized unknown. Total described in group unclear as some participants could have been counted twice given potential cross-over methodology. If assumed cross-over was undertaken for all, total randomized would be 34. Age of participants not given. Participants had variety of aetiological factors for cough (pneumonia, acute and chronic bronchitis, bronchiectasis, carcinoma, cardiac failure, cor pulmonale, nervous cough, coryza, influenza) Inclusion and exclusion criteria not described	
Interventions	Dimyrlil (active ingredient = isoaminile citrate, a codeine derivative) or placebo in identical bottles. Dose used varied. Initially 3 to 4 times/day followed by 'as necessary' dosing of up to 5 times a day (1 to 2 g)	
Outcomes	Outcomes not clearly specified. Paper stated: "The evidence of the patient, the several observers (day and night nurses, physician, and medico-social worker), the number of doses per 24 hours, and (when recorded) the actual cough frequencies were considered in deciding whether or not the nuisance and frequency of cough had been reduced"	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement

Azzopardi 1964 (Continued)

Random sequence generation (selection bias)	Unclear risk	Method not specified
Allocation concealment (selection bias)	Unclear risk	Method not specified
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo used and pharmacists not connected to trial involved
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Placebo used and pharmacists not connected to trial involved
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Outcome of drop-outs and withdrawals unclear
Selective reporting (reporting bias)	Unclear risk	Outcomes not clearly specified
Other bias	Unclear risk	Insufficient data to be certain

Principi 1986

Methods	<p>Multi-centre, double-blind, parallel, placebo-controlled RCT. Children recruited from 3 hospitals in Italy</p> <p>Potential participants admitted into hospital for symptoms of pneumonia screened for inclusion criteria (next row). Double-blinded study and all participants were treated as inpatients and re-evaluated daily for heart rate, respiratory rate and maximal rectal body temperature. Cough, dyspnoea and chest pathological scores also recorded daily. Chest X-ray on admission and end of treatment. Compliance not mentioned but presumed excellent given inpatient study</p> <p>All children given antibiotics (see column on intervention). Other co-treatment (e.g. anti-pyretic agents) not mentioned. Inclusion and exclusion criteria described in next column</p> <p>Description of withdrawals or drop-outs not mentioned. As children were inpatients, assumed most followed up. Chest X-ray follow-up rate 115/120 = 95.8%</p>
Participants	<p>Total of 120 children randomized - 60 in each arm. Outcome measure available for 115 children (57 active arm, 58 controls), 95.8%</p> <p>Antibiotic with ambroxol group: mean age not given, 11 aged < 1 year, 9 aged 1 to 2 years, 19 aged 2 to 5 years, 21 aged 5 to 12 years. Gender - M: 28; F: 32. Mean body weight 17.1 kg (SD 1.08)</p> <p>Antibiotic with placebo: mean age not given, 12 children aged < 1 year, 11 aged 1 to 2 years, 20 aged 2 to 5 years, 17 aged 5 to 12 years. Gender - M: 38; F: 22. Mean body weight 16.2 kg (SD 1.06)</p> <p>Inclusion criteria: children admitted into hospital for pneumonia. Have had blood culture performed before commencement of antibiotics and positive for well-defined bacterium or a chest X-ray showing lobar and sub lobar involvement, with erythrocyte sedimentation rate ≥ 30 mm/h and C-reactive protein ≥ 25 μg/mL</p>

Principi 1986 (Continued)

	Exclusion criteria: taken antibiotics, mucolytics or mucoregulatory drugs in the preceding week	
Interventions	Trial medications consisted of ambroxol (1.5 to 2 mg/kg/day in 2 divided doses) or placebo for 10 days. All children also given antibiotics, chosen on basis of microbiological data or in accordance with literature on most probable aetiology for each age, for 7 to 10 days. Children aged < 5 years given oral amoxil or intramuscular ampicillin (50 mg/kg in 3 to 4 divided doses). Older children had oral erythromycin ethylsuccinate (50 mg/kg/day in 4 doses)	
Outcomes	Cough, dyspnoea and chest pathological signs scored, ranging from 0 (absent) to 3 (very severe). Chest X-ray findings at the end of treatment was compared to pre-treatment chest X-ray and expressed as normalised, improved or unchanged	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not specified
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo used
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Placebo used
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-outs and withdrawals described
Selective reporting (reporting bias)	Low risk	Follow-up of > 90% of participants
Other bias	Unclear risk	Insufficient data to be certain

Methods	<p>Multi-centre, double-blind, parallel RCT comparing amoxicillin plus bromhexine versus amoxicillin alone. Participants recruited from 22 centres involving internalists or pulmonologists in the Philippines</p> <p>Potential participants evaluated for inclusion criteria by history, examination, CXR, laboratory tests (blood counts, sputum). The method of randomization and allocation was not described. Double-blinded study and all participants were treated as outpatients and re-evaluated on days 3, 5, 7 and 10. Compliance monitored by pill counting</p> <p>Participants allowed to receive medications for fever and constitutional symptoms but not any other cough expectorants or antimicrobials. Inclusion and exclusion criteria described in next column</p> <p>Description of withdrawals or drop-outs mentioned for entire group. Maximum follow-up rate 375/407 = 92% but less for other aspects</p>
Participants	<p>Total of 407 subjects randomized - 201 in active Rx and 206 in control group. 392 completed study (192 active, 200 controls). Compliance of 80% in active group and 85% in control group</p> <p>Amoxil with bromhexine group: mean age 32 (SD 13) years, gender - 117 M: 75 F; 51 with pneumonia, 141 with bronchitis</p> <p>Amoxil alone: mean age 32 (SD 12), gender - 130 M: 70 F; 50 with pneumonia, 150 with bronchitis</p> <p>Inclusion criteria: adolescents and adults aged 15 to 60 years with uncomplicated community-acquired lower respiratory tract infection (pneumonia or bronchitis), clinically assessed to be bacterial in aetiology. Pneumonia defined as presence of cough < 2 weeks, purulent phlegm, fever and/or leucocytosis (> 10,000 mm³) and pulmonary infiltrates on CXR. Acute bronchitis defined as presence of cough < 2 weeks, purulent phlegm, fever and/or leucocytosis (> 10,000 mm³). Sputum culture had to be sensitive to amoxil or if organism resistant, subject included if clinical response at Day 3 occurred on amoxil</p> <p>Exclusion criteria: frank respiratory failure, coexistent chronic disease (diabetes, renal failure, liver or renal impairment, terminal illness such as cancer, active tuberculosis, healed tuberculosis with bronchiectasis, chronic bronchitis or emphysema, heavy smokers (undefined)), pregnant or lactating, hypersensitivity to study drugs, or recent (< 2 weeks) treatment with antibiotics</p>
Interventions	<p>Active Rx = amoxil 240 mg and bromhexine 8 mg, both 4 times/day for 7 days</p> <p>Control group: amoxil alone, 250 mg 4 times/day for 7 days</p>
Outcomes	<p>Days 3, 5, 7 and 10. Participants evaluated for clinical response, bacteriological response, subjective symptom scores, adverse events, compliance, complete blood count</p> <p>Clinical response:</p> <p>Cured = complete disappearance of pre-treatment symptoms and signs</p> <p>Improvement = pre-treatment symptoms and signs improved but not cured</p> <p>Failure = pre-treatment symptoms and signs did not improve or worsened</p> <p>Indeterminate = clinical response could not be determined</p> <p>Clinical symptoms:</p> <p>10 mm visual analogue scale of symptoms of cough frequency, cough discomfort, difficulty breathing not related to cough, chest pain not related to cough, ease of expectoration</p> <p>Bacteriologic response:</p> <p>Eradication = absence of pre-treatment pathogen or no more culturable material could be expectorated</p>

Roa 1995 (Continued)

	Persistence = presence of pre-treatment pathogen Super-infection = appearance of resistant pathogen after starting treatment Indeterminate = bacteriologic response could not be reliably assessed	
Notes	Wrote to authors with no response Data for pneumonia alone available only for global clinical response outcome	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Data not provided
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo used
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Placebo used
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Follow-up in > 90% for some outcomes but less in others
Selective reporting (reporting bias)	Low risk	Outcomes of withdrawals and drop-outs mentioned
Other bias	Low risk	Insufficient data to be certain but multi-centre study from 22 centres, thus likely low

CXR: chest X-ray

F: female

M: male

Rx: treatment

RCT: randomized controlled trial

SD: standard deviation

tds: three times a day

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

Study	Reason for exclusion
Aliprandi 2004	Non-placebo trial. Study involves comparing levodropropizine, codeine and cloperastine to levocloperastine
Balli 2007	Erdosteine is not legally available as an over-the-counter medication in countries such as Australia, UK and USA. Study compared amoxil plus erdosteine to amoxil-placebo in children with acute lower respiratory tract infections
Barberi 1993	Non-placebo study comparing nimesulide to lysine-aspirin in children
Bartolucci 1981	Non-controlled study in 40 adults using anti-phlogistic-balsamic compound (in Italian)
Caporalini 2001	Non-placebo study comparing neltexine against N-acetylcysteine
Dotti 1970	Randomised controlled study but subjects did not have pneumonia (in Italian)
Finiguerra 1981	A double-blind study in adults with acute and chronic bronchitis (not pneumonia)
Forsell 1966	Non-placebo study comparing drops to syrup formulation of an antitussive in infants and young children (in German)
Hargrave 1975	Study examined role of bromhexine in prevention of postoperative pneumonia
Ida 1997	A review article describing 3 studies on dimemorfan, a dextromethorphan analogue. Of the 3 cited studies, one was a placebo-controlled trial. Insufficient details were included in the text and further data were not available from the author, who could not be contacted
Jayaram 2000	Non-placebo study comparing 2 cough formulations
Mancini 1996	The paper summarises 3 studies which were not referenced. The first of the 3 studies described a RCT in children with "acute lower respiratory affections (e.g. acute bronchitis, bronchoalveolitis)". Unknown if children with pneumonia included and results stated reduction in cough scores with no specific data given. We wrote to authors and no response was received The other 2 studies described were in adults with "superinfected chronic bronchitis" and "hypersecretory chronic obstructive bronchopneumopathies"
Pelucco 1981	Non-randomised, non-placebo study in 26 adults (in Italian)
Titti 2000	Erdosteine is not legally available as an over-the-counter medication in countries such as Australia, UK and USA. Multi-centre RCT compared ampicillin plus erdosteine to ampicillin-placebo in children with acute lower respiratory tract infections
Turrisi 1984	Non-randomised, non-placebo study using fenspiride in 20 adults (in Italian)
Wang 2005	Study used Fuxiong plaster (i.e. not an OTC medication). Randomised controlled study in children with pneumonia
Wieser 1973	Placebo but non-randomised study comparing placebo to prenodiazine in 84 adults (in German)

(Continued)

Zhang 2005	Study used Toubiao Qingfei (an externally applied therapy, i.e. not an OTC medication). Randomised controlled study in children with fever from pneumonia
Zurcher 1966	Non-placebo, double-blind study comparing Sinecod-Hommel to a codeine-based antitussive in 95 adults (in German)

OTC: over-the-counter

RCT: randomized controlled trial

DATA AND ANALYSES

Comparison 1. Children - global assessment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Not cured or not improved	1	120	Odds Ratio (M-H, Fixed, 95% CI)	0.40 [0.10, 1.62]
2 Not improved	1	120	Odds Ratio (M-H, Fixed, 95% CI)	0.40 [0.10, 1.62]
3 Not cured	1	120	Odds Ratio (M-H, Fixed, 95% CI)	0.36 [0.16, 0.77]

Comparison 2. Children - cough score

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean cough score at day 3	1	120	Mean Difference (IV, Fixed, 95% CI)	-0.25 [-0.33, -0.17]
2 Mean score at day 10	1	120	Mean Difference (IV, Fixed, 95% CI)	-0.15 [-0.17, -0.13]

Comparison 3. Adults - global assessment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Not cured or not improved	1	101	Odds Ratio (M-H, Fixed, 95% CI)	1.21 [0.48, 3.04]
2 Not improved	1	101	Odds Ratio (M-H, Fixed, 95% CI)	1.21 [0.48, 3.04]
3 Not cured	1	101	Odds Ratio (M-H, Fixed, 95% CI)	0.32 [0.13, 0.75]

Comparison 4. Combined children and adults

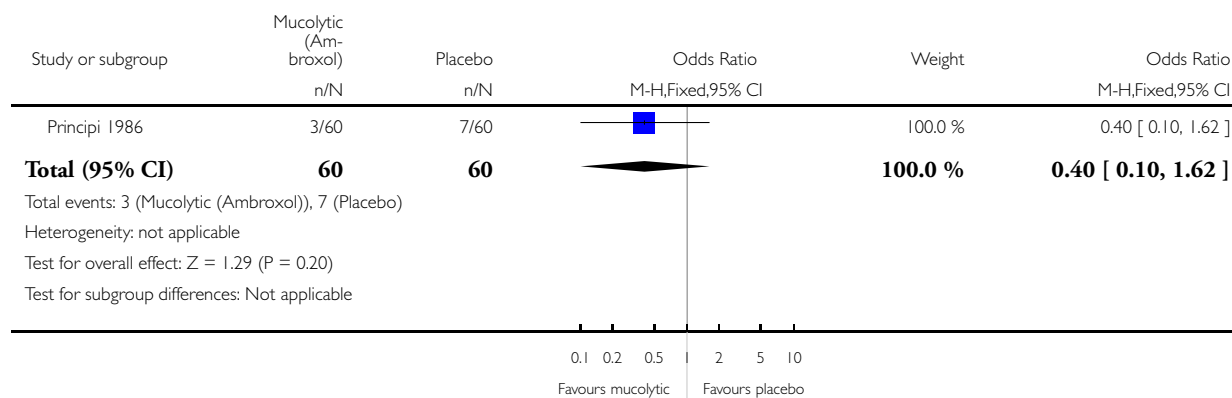
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Not cured or not improved	2	221	Odds Ratio (M-H, Fixed, 95% CI)	0.85 [0.40, 1.80]
2 Not improved	2	221	Odds Ratio (M-H, Fixed, 95% CI)	0.80 [0.38, 1.67]
3 Not cured	2	221	Odds Ratio (M-H, Fixed, 95% CI)	0.34 [0.19, 0.60]

Analysis 1.1. Comparison 1 Children - global assessment, Outcome 1 Not cured or not improved.

Review: Over-the-counter (OTC) medications to reduce cough as an adjunct to antibiotics for acute pneumonia in children and adults

Comparison: 1 Children - global assessment

Outcome: 1 Not cured or not improved

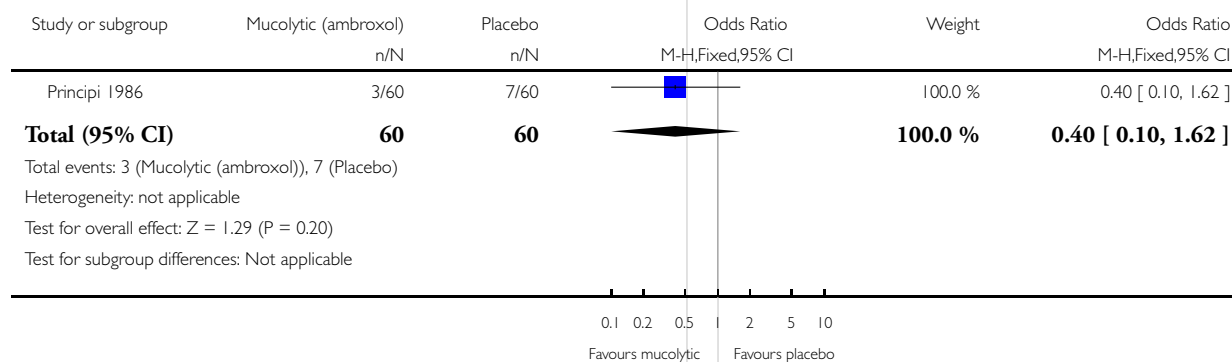


Analysis 1.2. Comparison 1 Children - global assessment, Outcome 2 Not improved.

Review: Over-the-counter (OTC) medications to reduce cough as an adjunct to antibiotics for acute pneumonia in children and adults

Comparison: 1 Children - global assessment

Outcome: 2 Not improved

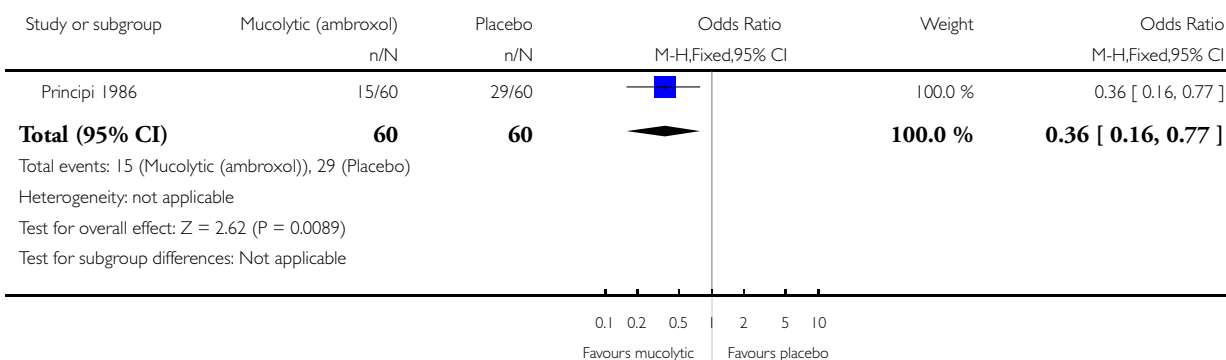


Analysis 1.3. Comparison 1 Children - global assessment, Outcome 3 Not cured.

Review: Over-the-counter (OTC) medications to reduce cough as an adjunct to antibiotics for acute pneumonia in children and adults

Comparison: 1 Children - global assessment

Outcome: 3 Not cured

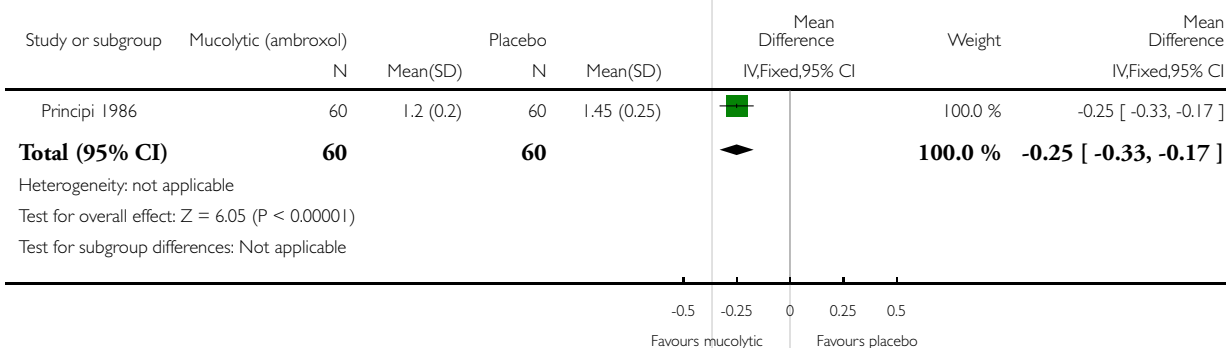


Analysis 2.1. Comparison 2 Children - cough score, Outcome 1 Mean cough score at day 3.

Review: Over-the-counter (OTC) medications to reduce cough as an adjunct to antibiotics for acute pneumonia in children and adults

Comparison: 2 Children - cough score

Outcome: 1 Mean cough score at day 3

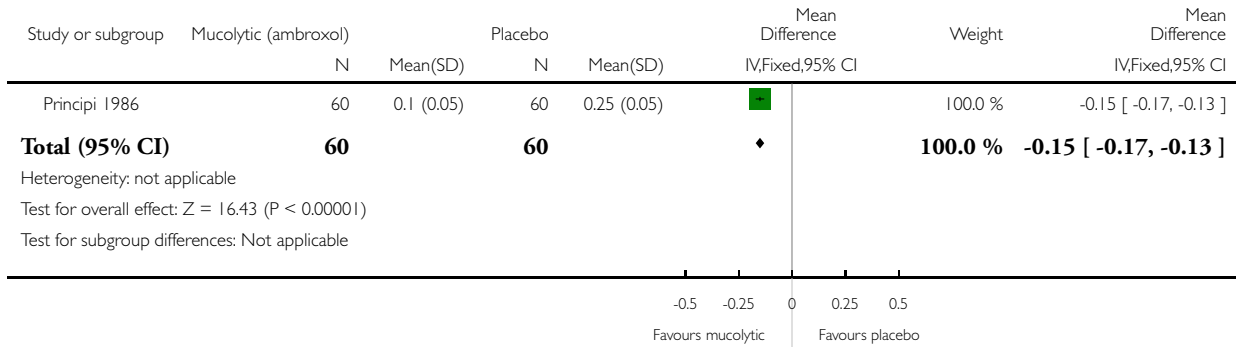


Analysis 2.2. Comparison 2 Children - cough score, Outcome 2 Mean score at day 10.

Review: Over-the-counter (OTC) medications to reduce cough as an adjunct to antibiotics for acute pneumonia in children and adults

Comparison: 2 Children - cough score

Outcome: 2 Mean score at day 10

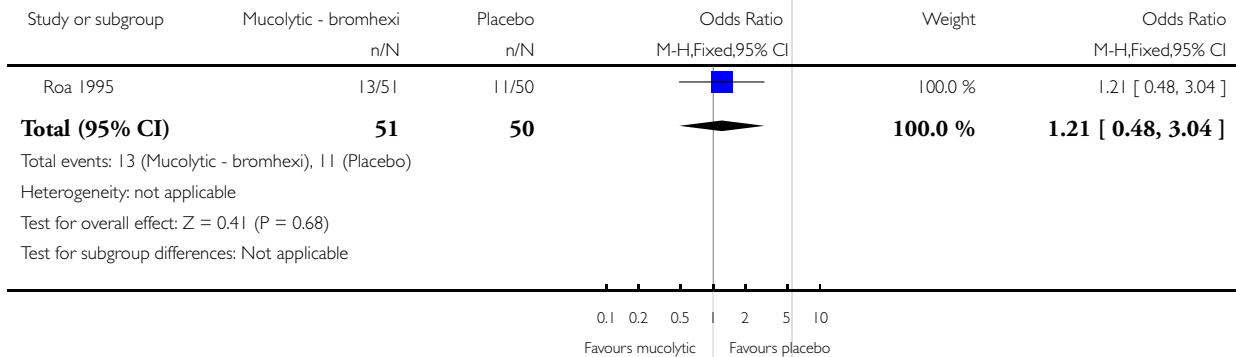


Analysis 3.1. Comparison 3 Adults - global assessment, Outcome 1 Not cured or not improved.

Review: Over-the-counter (OTC) medications to reduce cough as an adjunct to antibiotics for acute pneumonia in children and adults

Comparison: 3 Adults - global assessment

Outcome: 1 Not cured or not improved

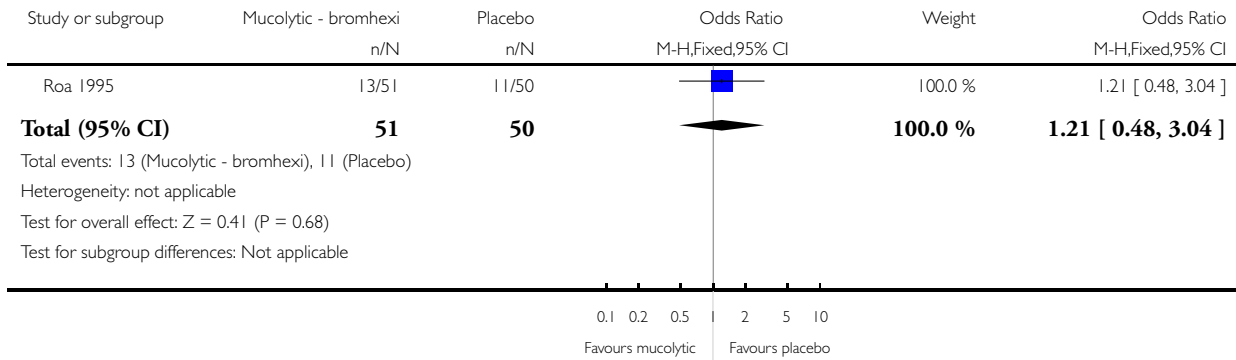


Analysis 3.2. Comparison 3 Adults - global assessment, Outcome 2 Not improved.

Review: Over-the-counter (OTC) medications to reduce cough as an adjunct to antibiotics for acute pneumonia in children and adults

Comparison: 3 Adults - global assessment

Outcome: 2 Not improved

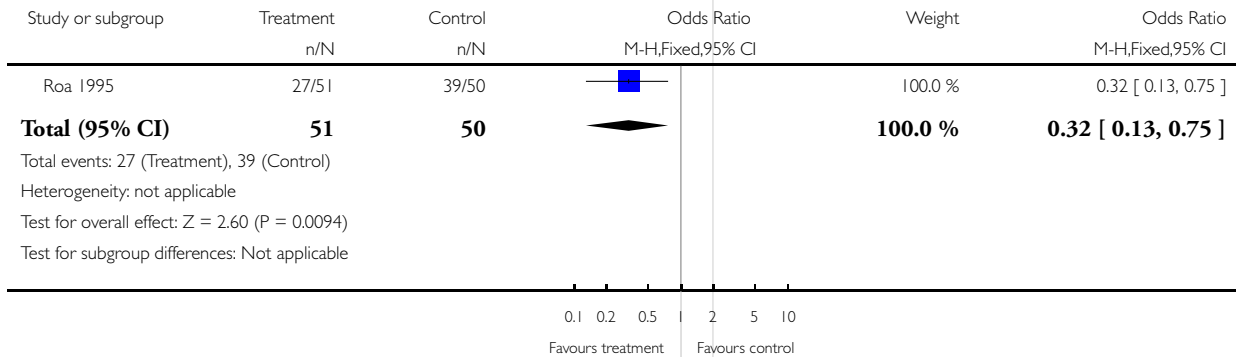


Analysis 3.3. Comparison 3 Adults - global assessment, Outcome 3 Not cured.

Review: Over-the-counter (OTC) medications to reduce cough as an adjunct to antibiotics for acute pneumonia in children and adults

Comparison: 3 Adults - global assessment

Outcome: 3 Not cured

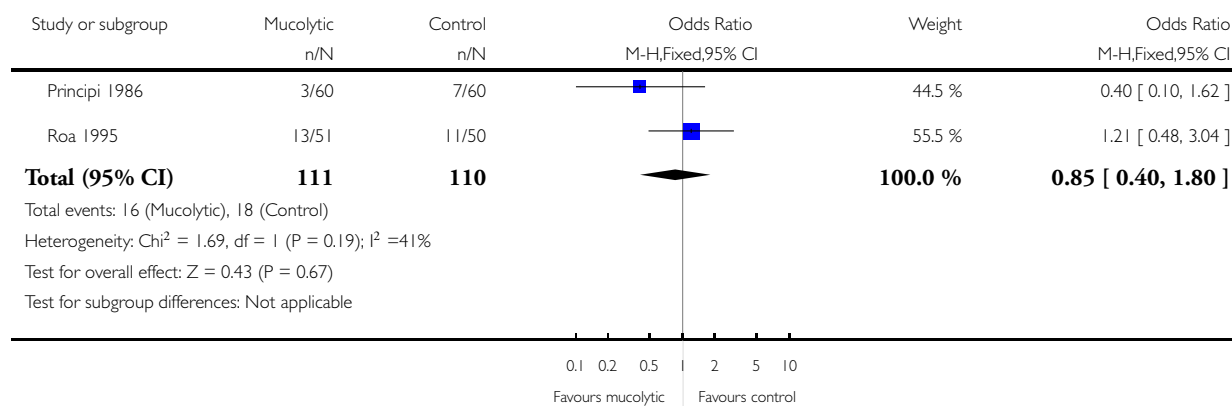


Analysis 4.1. Comparison 4 Combined children and adults, Outcome 1 Not cured or not improved.

Review: Over-the-counter (OTC) medications to reduce cough as an adjunct to antibiotics for acute pneumonia in children and adults

Comparison: 4 Combined children and adults

Outcome: 1 Not cured or not improved

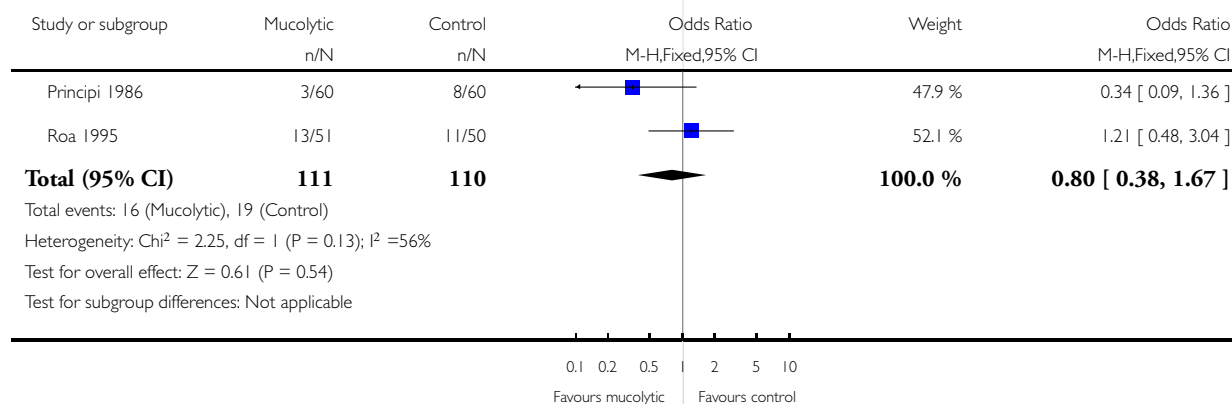


Analysis 4.2. Comparison 4 Combined children and adults, Outcome 2 Not improved.

Review: Over-the-counter (OTC) medications to reduce cough as an adjunct to antibiotics for acute pneumonia in children and adults

Comparison: 4 Combined children and adults

Outcome: 2 Not improved

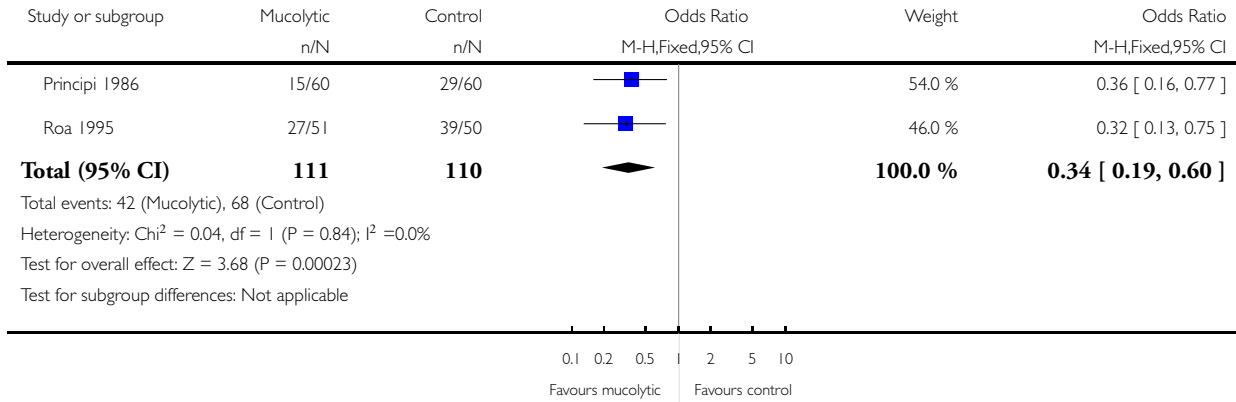


Analysis 4.3. Comparison 4 Combined children and adults, Outcome 3 Not cured.

Review: Over-the-counter (OTC) medications to reduce cough as an adjunct to antibiotics for acute pneumonia in children and adults

Comparison: 4 Combined children and adults

Outcome: 3 Not cured



APPENDICES

Appendix I. Previous search strategy

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2009, Issue 2) which contains the Acute Respiratory Infections Group's Specialised Register; MEDLINE (January 1966 to July Week 1, 2009); OLDMEDLINE (1950 to 1965); EMBASE (1980 to July 2009).

The following search strategy was run in MEDLINE and CENTRAL and adapted for EMBASE.

MEDLINE (OVID)

- 1 exp Cough/
- 2 cough.mp.
- 3 or/1-2
- 4 exp Pneumonia/
- 5 pneumonia.mp.
- 6 or/4-5
- 7 exp Antitussive Agents/
- 8 antitussive agent\$.mp.
- 9 exp Expectorants/
- 10 expectorant\$.mp.
- 11 exp Cholinergic Antagonists/
- 12 cholinergic antagonist\$.mp.
- 13 exp Histamine H1 Antagonists/
- 14 histamine H1 antagonist\$.mp.
- 15 mucolytic\$.mp.

- 16 exp Drug Combinations/
- 17 drug combination\$.mp.
- 18 exp Drugs, Non-Prescription/
- 19 non prescription drug\$.mp.
- 20 (over-the-counter or over the counter or OTC).mp.
- 21 or/7-20
- 22 3 and 6 and 21

EMBASE.com search strategy

- 1. 'coughing'/exp
 - 2. cough*:ti,ab
 - 3. #1 OR #2
 - 4. 'pneumonia'/exp
 - 5. pneumon*:ti,ab
 - 6. #4 OR #5
 - 7. 'antitussive agent'/exp
 - 8. antitussiv*:ti,ab
 - 9. 'expectorant agent'/exp
 - 10. expectorant*:ti,ab
 - 11. 'cholinergic receptor blocking agent'/exp
 - 12. 'cholinergic antagonist':ti,ab OR 'cholinergic antagonists':ti,ab
 - 13. 'histamine h1 receptor antagonist'/exp
 - 14. 'histamine h1 antagonist':ti,ab OR 'histamine h1 antagonists':ti,ab
 - 15. 'mucolytic agent'/exp
 - 16. mucolytic*:ti,ab
 - 17. 'drug combination'/exp
 - 18. 'drug combination':ti,ab OR 'drug combinations':ti,ab
 - 19. 'non prescription drug'/exp
 - 20. 'non prescription drug':ti,ab OR 'non prescription drugs':ti,ab OR 'non-prescription drug':ti,ab OR 'non-prescription drugs':ti,ab
 - 21. 'over the counter':ti,ab OR 'over-the-counter':ti,ab OR otc:ti,ab
 - 22. #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21
 - 23. #3 AND #6 AND #22
- There were no language or publication restrictions.

Appendix 2. Embase.com search strategy

- #31. #27 AND #30 114 8 Aug 2011
- #30. #28 OR #29 883,082 8 Aug 2011
- #29. random*:ab,ti OR placebo*:ab,ti OR factorial*:ab,ti OR crossover*:ab,ti OR 'cross-over':ab,ti OR 'cross over':ab,ti OR volunteer*:ab,ti OR assign*:ab,ti OR allocat*:ab,ti OR ((singl* OR doubl*) NEAR/1 blind*):ab,ti AND [embase]/lim 842,895 8 Aug 2011
- #28. 'randomized controlled trial'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp AND [embase]/lim 246,402 8 Aug 2011
- #27. #7 AND #26 771 8 Aug 2011
- #26. #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 360,086 8 Aug 2011
- #25. (cough* NEAR/3 (suppress* OR mixture* OR syrup* OR medicine* OR remed* OR relief* OR formula*)):ab,ti AND [embase]/lim 825 8 Aug 2011
- #24. 'over-the-counter':ab,ti OR 'over the counter':ab,ti OR otc:ab,ti AND [embase]/lim 6,613 8 Aug 2011
- #23. (('non prescption' OR 'non prescribed') NEAR/3 (drugs* OR medicine* OR medicat* OR pharmaceut*)):ab,ti AND [embase]/lim 115 8 Aug 2011

- #22. ((nonprescribed OR nonprescription) NEAR/3 (drug* OR medicine* OR pharmaceut* OR medicat*)):ab,ti AND [embase]/lim 515 8 Aug 2011
- #21. 'non prescription drug'/de AND [embase]/lim 5,514 8 Aug 2011
- #20. (drug* NEAR/2 combination*):ab,ti AND [embase]/lim 12,426 8 Aug 2011
- #19. 'drug combination'/exp AND [embase]/lim 96,985 8 Aug 2011
- #18. mucolytic*:ab,ti AND [embase]/lim 1,182 8 Aug 2011
- #17. 'mucolytic agent'/exp AND [embase]/lim 45,629 8 Aug 2011
- #16. antihistamin*:ab,ti OR 'anti-histamine':ab,ti OR 'anti-histamines':ab,ti OR 'histamine h1 antagonist':ab,ti OR 'histamine h1 antagonists':ab,ti AND [embase]/lim 10,403 8 Aug 2011
- #15. 'histamine h1 receptor antagonist'/exp AND [embase]/lim 78,664 8 Aug 2011
- #14. anticholinergic*:ab,ti OR 'anti-cholinergic':ab,ti OR 'anti-cholinergics':ab,ti AND [embase]/lim 9,864 8 Aug 2011
- #13. (cholinergic NEAR/2 (blocking OR antagonist*)):ab,ti AND [embase]/lim 1,317 8 Aug 2011
- #12. 'cholinergic receptor blocking agent'/exp AND [embase]/lim 119,061 8 Aug 2011
- #11. expectorant*:ab,ti AND [embase]/lim 544 8 Aug 2011
- #10. 'expectorant agent'/exp AND [embase]/lim 17,848 8 Aug 2011
- #9. antitussiv*:ab,ti AND [embase]/lim 1,277 8 Aug 2011
- #8. 'antitussive agent'/de AND [embase]/lim 2,479 8 Aug 2011
- #7. #3 AND #6 8,334 8 Aug 2011
- #6. #4 OR #5 168,614 8 Aug 2011
- #5. pneumon*:ab,ti OR bronchopneumon*:ab,ti AND [embase]/lim 106,283 8 Aug 2011
- #4. 'pneumonia'/exp AND [embase]/lim 120,145 8 Aug 2011
- #3. #1 OR #2 48,243 8 Aug 2011
- #2. cough*:ab,ti AND [embase]/lim 28,592 8 Aug 2011
- #1. 'coughing'/de OR 'irritative coughing'/de AND [embase]/lim 37,461 8 Aug 2011

Appendix 3. CINAHL (Ebsco) search strategy

S29 S7 and S27 3

S28 S7 and S27 17

S27 S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 20670

S26 TI (cough* mixtur* or cough* medicin* or cough* suppress* or cough* relief* or cough* remed* or cough* formul* or cough* syrup*) OR AB (cough* mixtur* or cough* medicin* or cough* suppress* or cough* relief* or cough* remed* or cough* formul* or cough* syrup*) 158

S25 TI (over the counter or over-the-counter or otc) OR AB (over the counter or over-the-counter or otc) 1886

S24 TI (nonprescribed drug* or non-prescribed drug* or nonprescribed medicin* or non-prescribed medicin* or nonprescribed pharmaceut* or non-prescribed pharmaceut* or nonprescribed medicat* or non-prescribed medicat*) OR AB (nonprescribed drug* or non-prescribed drug* or nonprescribed medicin* or non-prescribed medicin* or nonprescribed pharmaceut* or non-prescribed pharmaceut* or nonprescribed medicat* or non-prescribed medicat*) 28

S23 TI (nonprescription drug* or non-prescription drug* or nonprescription medicin* or non-prescription medicin* or nonprescription pharmaceut* or non-prescription pharmaceut* or nonprescription medicat* or non-prescription medicat*) OR AB (nonprescription drug* or non-prescription drug* or nonprescription medicin* or non-prescription medicin* or nonprescription pharmaceut* or non-prescription pharmaceut* or nonprescription medicat* or non-prescription medicat*) 203

S22 (MH "Drugs, Non-Prescription") 2150

S21 TI drug* N2 combination* OR AB drug* N2 combination* 1061

S20 (MH "Drug Combinations+") 8745

S19 TI mucolytic* OR AB mucolytic* 77

S18 TI histamin* h1 antagonist* OR AB histamin* h1 antagonist* 33

S17 TI (antihistamin* or anti-histamin*) OR AB (antihistamin* or anti-histamin*) 775

S16 (MH "Histamine H1 Antagonists+") 1680

S15 TI (anticholinergic* or anti-cholinergic*) OR AB (anticholinergic* or anti-cholinergic*) 799

S14 TI cholinergic N2 antagonist* OR AB cholinergic N2 antagonist* 11

S13 TI cholinergic N2 blocking OR AB cholinergic N2 blocking 4
 S12 (MH "Cholinergic Antagonists+") 2328
 S11 TI expectorant* OR AB expectorant* 20
 S10 (MH "Expectorants+") 633
 S9 TI antitussiv* OR AB antitussiv* 64
 S8 (MH "Antitussive Agents+") 3205
 S7 S3 and S6 370
 S6 S4 or S5 1827
 S5 TI (pneumon* or bronchopneumon*) OR AB (pneumon* or bronchopneumon*) 8848
 S4 (MH "Pneumonia+") 7395
 S3 S1 or S2 4246
 S2 TI cough* OR AB cough* 3599
 S1 (MH "Cough") 1927

Appendix 4. LILACS (BRIEME) search strategy

Mh nonprescription drugs OR Tw nonprescrip\$ OR Tw nonprescribed OR Tw Medicamentos sin Prescripción OR Tw Medicamentos sem Prescrição OR Tw over-the-counter OR Tw otc OR Mh Drug Combinations OR Tw drug combination\$ OR Tw Combinación de Medicamentos OR Tw Combinação de Medicamentos OR Mh Antitussive Agents OR Tw antitussiv\$ OR Tw Agentes Antitusígenos OR Tw Antitusígenos OR Mh Expectorants OR Tw expectorant\$ OR Mh Cholinergic Antagonists OR Tw Antagonistas Colinérgicos OR Tw Antagonistas Colinérgicos OR Tw anticholinergic\$ OR Tw cholinergic blocking OR Tw cholinergic antagonist\$ OR Tw antagonist\$ Colinérgic\$ OR Mh Histamine H1 Antagonists OR Tw antihistamin\$ OR Tw Antagonistas de Histamina H1 OR Tw Antagonistas dos Receptores H1 de Histamina OR Tw mucolytic\$

Appendix 5. Web of Science (Thomson ISI) search strategy

Topic=(cough*) AND Topic=(pneumon* or bronchopneumon*) AND Topic=(antitussiv* or expectorant* or cholinergic antagonist* or histamin* h1 antagonist* or antihistamin* or mucolytic* or nonprescription* or nonprescribed* or over-the-counter or otc) Timespan=2009-2011. Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH.

WHAT'S NEW

Last assessed as up-to-date: 8 August 2011.

Date	Event	Description
8 August 2011	New search has been performed	Searches conducted. No new trials were identified for inclusion in this update
8 August 2011	New citation required but conclusions have not changed	Our conclusions remain unchanged.

HISTORY

Protocol first published: Issue 3, 2006

Review first published: Issue 4, 2007

Date	Event	Description
10 July 2009	New search has been performed	Searches conducted. No new included studies found. Two new studies excluded
21 February 2008	Amended	'Summary of findings' table added.
30 January 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

The protocol was written by Christina C Chang (CCC), Anne B Chang (ABC) and Allen C Cheng (ACC) based on previous protocols on cough in children.

For the review: CCC and ABC selected articles from search, performed the data extraction, data analysis and wrote the review.

ACC was the adjudicator if disagreement occurred and contributed to writing the review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- NHMRC, Australia.
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- Queensland Health Smart State Funds, Australia.
Salary support for ABC

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Anti-Bacterial Agents [*therapeutic use]; Antitussive Agents [*therapeutic use]; Chemotherapy, Adjuvant [methods]; Cough [*drug therapy; etiology]; Drug Therapy, Combination [methods]; Expectorants [therapeutic use]; Nonprescription Drugs [*therapeutic use]; Pneumonia [complications; *drug therapy]; Randomized Controlled Trials as Topic; Treatment Outcome

MeSH check words

Adolescent; Adult; Child; Humans