Cochrane Library

Cochrane Database of Systematic Reviews

Acetylcysteine and carbocysteine for acute upper and lower respiratory tract infections in paediatric patients without chronic broncho-pulmonary disease (Review)

Chalumeau M, Duijvestijn YCM

Chalumeau M, Duijvestijn YCM.
Acetylcysteine and carbocysteine for acute upper and lower respiratory tract infections in paediatric patients without chronic broncho-pulmonary disease.
Cochrane Database of Systematic Reviews 2013, Issue 5. Art. No.: CD003124.
DOI: 10.1002/14651858.CD003124.pub4.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Acetylcysteine and carbocysteine for acute upper and lower respiratory tract infections in paediatric patients without chronic broncho-pulmonary disease

Martin Chalumeau[1], Yvonne CM Duijvestijn[2]

[1]INSERM U953 and Department of Pediatrics, Necker Hospital, AP-HP and Paris Descartes University, Paris, France. [2]Department of Paediatrics (119), Medical Centre Alkmaar, Alkmaar, Netherlands

Contact: Martin Chalumeau, INSERM U953 and Department of Pediatrics, Necker Hospital, AP-HP and Paris Descartes University, Paris, France. martin.chalumeau@gmail.com, martin.chalumeau@nck.aphp.fr.

Editorial group: Cochrane Acute Respiratory Infections Group.
Publication status and date: New search for studies and content updated (no change to conclusions), comment added to review, published in Issue 5, 2013.

Citation: Chalumeau M, Duijvestijn YCM. Acetylcysteine and carbocysteine for acute upper and lower respiratory tract infections in paediatric patients without chronic broncho-pulmonary disease. *Cochrane Database of Systematic Reviews* 2013, Issue 5. Art. No.: CD003124. DOI: 10.1002/14651858.CD003124.pub4.

ABSTRACT

Background

Acetylcysteine and carbocysteine are the most commonly prescribed mucolytic drugs in Brazil and many European and African countries. To our knowledge, no systematic review has been published on their efficacy and safety for acute upper and lower respiratory tract infections (RTIs) in children without chronic broncho-pulmonary disease.

Objectives

The objective was to assess the efficacy and safety and to establish a benefit-risk ratio of acetylcysteine and carbocysteine as symptomatic treatments for acute upper and lower RTIs in paediatric patients without chronic broncho-pulmonary disease.

Search methods

We searched CENTRAL (2013, Issue 2), MEDLINE (1966 to February week 3, 2013), EMBASE (1980 to March 2013), Micromedex (2010), Pascal (1987 to 2004) and Science Citation Index (1974 to March 2013).

Selection criteria

To study efficacy, we used randomised controlled trials (RCTs) comparing the use of acetylcysteine or carbocysteine versus placebo, either alone or as an add-on therapy. To study safety, we used trials comparing acetylcysteine or carbocysteine versus active treatment or no treatment and case reports.

Data collection and analysis

In this review update two review authors (YD, MC), with help from a colleague, extracted data and assessed trial quality. We performed a subgroup analysis of children younger than two years of age.

Main results

We included six trials involving 497 participants to study efficacy. They showed some benefit (e.g. reduction of cough at day seven) from mucolytic agents, although differences were of little clinical relevance. No conclusion was drawn about the subgroup of infants younger than two years because data were unavailable. Thirty-four studies, including the previous six trials involving 2064 children, were eligible

to study safety. Overall safety was good but very few data were available to evaluate safety in infants younger than two years. However, 59 cases of paradoxically increased bronchorrhoea observed in infants were reported to the French pharmacovigilance system.

Authors' conclusions

The results have to be interpreted with caution because they are based on a limited number of participants included in studies whose methodological quality is questionable. Acetylcysteine and carbocysteine seem to have a limited efficacy and appear to be safe in children older than two years. These results should take into consideration the fact that acetylcysteine and carbocysteine are prescribed for self limiting diseases (for example, acute cough, bronchitis). Given strong concerns about safety, these drugs should only be used for acute upper and lower RTIs in the context of a RCT with regards to children younger than two years.

PLAIN LANGUAGE SUMMARY

Acetylcysteine and carbocysteine to treat acute upper and lower respiratory tract infections in children without chronic broncho-pulmonary disease

Acetylcysteine and carbocysteine are the most commonly prescribed drugs which aim to change the structure of bronchial secretions. This systematic review assessed their efficacy and safety for treating acute upper and lower respiratory tract infections in children without chronic broncho-pulmonary disease. We also looked in particular at patients younger than two years of age.

Forty-nine trials met the inclusion criteria. Six trials involving 497 participants were included to study efficacy, and compared acetylcysteine or carbocysteine to placebo. Thirty-four trials (including the previous six) were eligible to study safety and involved 2064 paediatric patients.

The results of this review suggest actual but limited efficacy of acetylcysteine and carbocysteine (e.g. reduction of cough at day seven) and good overall safety (except for rare mild gastrointestinal side effects) among children older than two years of age. However, the number of participants included was limited and the methodological quality was questionable. These results should also take into consideration the fact that acetylcysteine and carbocysteine are prescribed for self limiting diseases (for example, acute cough, bronchitis). In children younger than two years, and given strong concerns about safety (increased instead of decreased bronchial secretions), these drugs should only be used for acute upper and lower respiratory tract infections in the context of a randomised controlled trial.

BACKGROUND

Description of the condition

Acute upper and lower respiratory tract infections (RTIs) are the most frequent infections in children, occurring 7 to 10 times a year in school age children (Chang 2006; Shields 2008). The main symptom is acute cough. Coughing can last more than 10 days in half of the cases and more than three weeks in about 10% of cases. Coughing can be distressing, especially in very young children and it has a major impact on the child's and other family members' sleep, and can cause parental anxiety (Shields 2008). Parents frequently seek drugs (over-the-counter drugs or drugs requiring a medical prescription) to treat their children's cough.

Description of the intervention

Of the mucolytic drugs available to treat acute upper and lower RTI, the cysteine derivatives (that is, acetylcysteine and carbocysteine) are the most commonly prescribed in many European (Cano Garcinuño 2013; Chalumeau 2000; Duijvestijn 1997; Sen 2011) and African countries (Mourdi 2010) and in Brazil (Bricks 1996). Various systemic (oral, intramuscular or intravenous) or inhaled forms of the drugs are available. In The Netherlands, one-third of general practitioners prescribe acetylcysteine for asthmatic bronchitis, acute bronchitis, or for productive or dry cough (Duijvestijn 1997; Sen 2011). In France, three studies have shown that acetylcysteine and carbocysteine are some of the most prescribed drugs for children, especially those younger than two years of age (Chalumeau 2000; Collet 1991; Horen 2002). In one of these studies, cysteine derivatives accounted for 18% to 25% of drug prescriptions for acute rhinopharyngitis, acute cough and acute bronchitis (Chalumeau 2000). The high rate of prescription of cysteine derivatives for acute upper and lower RTI in paediatric patients was shown to be unchanged in the last decade in France (Halna 2005). In Italy, carbocysteine is one of the 20 drugs most prescribed by family paediatricians (Cazzato 2001; Sen 2011). In Spain, expectorants are the drugs most prescribed by paediatricians and general practitioners for the treatment of acute bronchitis, and they are the second commonest pharmacological group prescribed to children under two years of age (Cano Garcinuño 2013; Sanz 1988). In Germany, acetylcysteine is in the top five of drugs prescribed to paediatric patients under one year of age (Bücheler 2002).

How the intervention might work

In vitro, cysteine derivatives act by breaking disulphide bridges between macromolecules, which leads to a reduction in mucus viscosity (Medici 1979). This property led physicians in the 1960s and 1970s to develop mucolytic drugs for clinical situations where sputum modification to reduce cough is sought, including cystic fibrosis and chronic and acute bronchitis. In adult patients, the use of cysteine derivatives may cause a small reduction in acute exacerbations of chronic bronchitis (Poole 2012). In paediatric patients with cystic fibrosis, there is no evidence of effectiveness of either oral or inhaled administration of acetylcysteine (Duijvestijn 1999). In addition to being used for patients with severe chronic pulmonary disease, in some countries cysteine derivatives are also widely used to treat previously healthy paediatric patients with acute broncho-pulmonary disease.

Why it is important to do this review

To our knowledge, no systematic review has been previously published on the efficacy and safety of acetylcysteine and carbocysteine for acute upper and lower RTIs in paediatric patients without chronic broncho-pulmonary disease.

OBJECTIVES

1. To assess the efficacy of acetylcysteine and carbocysteine as symptomatic treatments for acute upper and lower RTIs in paediatric patients without chronic broncho-pulmonary disease.
2. To evaluate the safety of acetylcysteine and carbocysteine in the symptomatic treatment of acute upper and lower RTIs in paediatric patients without chronic broncho-pulmonary disease.
3. To establish a benefit-risk ratio for the use of acetylcysteine and carbocysteine as symptomatic treatments for acute upper and lower RTIs in paediatric patients without chronic broncho-pulmonary disease.

METHODS

Criteria for considering studies for this review

Types of studies

To study efficacy, we used randomised controlled trials (RCTs) comparing the systemic or inhaled use of acetylcysteine and/or carbocysteine versus placebo, either alone or as an add-on therapy (see Types of interventions).

To study safety, we also used trials comparing acetylcysteine and/or carbocysteine versus active treatment or no treatment and case reports.

Types of participants

We included trials regardless of gender and study setting (ambulatory or hospital-based). We included trials if the participants met all of the following criteria.

1. Younger than 18 years (when studies involved adults and children, a minimum of 50% (arbitrary) of children were retained as a threshold to include the study).
2. Treated in primary, secondary or tertiary care settings.
3. Physician diagnosis of respiratory tract infection (RTI): acute pneumonia, acute bronchitis, acute bronchiolitis (secondary to respiratory syncytial virus or to another virus) or acute cough (including pertussis).
4. Duration of symptoms less than four weeks.

We excluded trials which included patients with any of the following conditions.

1. Acetaminophen (paracetamol) intoxication.
2. Bronchiectasis, cystic fibrosis or broncho-pulmonary dysplasia.
3. Underlying immunodeficiency or respiratory tract anatomical defect.
4. Acute respiratory distress requiring mechanical ventilation.

We included trials which involved patients with underlying asthma or tuberculosis (as defined by the investigators).

Types of interventions

We included trials assessing the systemic use (that is, oral, intramuscular or intravenous) or inhaled use of acetylcysteine or carbocysteine, regardless of the dose regimen.

In order to study efficacy, we included trials which allowed concurrent use of other treatments (such as antibiotics, corticosteroids, bronchodilators, antitussives, chest physiotherapy, analgesics or antipyretics), if they allowed equal access to such medications for patients in the intervention and control groups.

We included trials comparing the use of acetylcysteine or carbocysteine in association with other treatments (such as antibiotics, corticosteroids, bronchodilators, antitussives, chest physiotherapy, analgesics or antipyretics) versus placebo, active treatment or no treatment, as well as case reports to study the safety of acetylcysteine or carbocysteine in association with other treatments.

Types of outcome measures

We included trials reporting at least one of the following outcome measures.

Primary outcomes

1. Time to resolution of clinical symptoms, signs or both (where clinical symptoms and signs may include increased respiratory rate, use of accessory respiratory muscles, abnormal lung examination, cough, sputum production, fever or activity limitations).
2. Proportions of patients with clinical symptoms, signs or both at a designated time.
3. Global assessment of improvement by clinicians, patients or their parents at a designated time.

Secondary outcomes

1. Reduced hospitalisation rates or duration, or both, of hospitalisation stay.
2. Adverse events reported by the investigators.

Search methods for identification of studies

Electronic searches

For this update we searched the Cochrane Central Register of Controlled Trials (CENTRAL) 2013, Issue 2, part of *The Cochrane Library,* www.thecochranelibrary.com (accessed 6 March 2013), which contains the Cochrane Acute Respiratory Infections (ARI) Group's Specialised Register; MEDLINE (January 2008 to February week 3, 2013); EMBASE (January 2008 to March 2013) and Web of Science (2008 to March 2013). (See Appendix 1 for the MEDLINE and CENTRAL search terms).

We combined the MEDLINE search with a filter based on the work of Boluyt 2008 to identify child studies. We adapted the search terms to search EMBASE (see Appendix 2) and Web of Science (see Appendix 3). For details of previous searches see Appendix 4.

Searching other resources

We handsearched the references of trials obtained to identify other relevant studies. We contacted trial authors for additional information if required, and we requested information on unpublished trials from drug companies that manufacture acetylcysteine or carbocysteine in France, The Netherlands and the United States. We imposed no language or publication restrictions.

Data collection and analysis

Selection of studies

In the first publication of our review (Duijvestijn 2009), three review authors (YD, MC, John Smucny) independently searched titles and abstracts to identify potentially relevant articles. We obtained full-text versions of these articles and articles with ambiguous titles or abstracts. The same three review authors independently selected articles which fulfilled the inclusion criteria. We resolved discrepancies regarding inclusion criteria by discussion. In this 2012 update, two review authors (YD, MC), with help from a colleague (TA), independently searched titles and abstracts to identify potentially relevant articles.

Data extraction and management

In the first published version of our review (Duijvestijn 2009), three review authors (YD, MC, John Smucny) independently extracted data from each study using electronic data collection forms. We resolved disagreements through discussion. In this 2012 update, two review authors (YD, MC) independently extracted data.

Assessment of risk of bias in included studies

Two review authors (YD, MC), with external help of a colleague (TA), independently graded the quality of each included study using The Cochrane Collaboration's tool for assessing risk of bias (RevMan 2012). We resolved disagreements by discussion and consensus. The support for judgement came from a single published or unpublished study report in all cases. We incorporated the results of the 'Risk of bias' assessment into the results.

Measures of treatment effect

We calculated risk ratios (RR) and risk differences (RDs) for dichotomous outcome variables of each individual study. We calculated the summary weighted RDs and their 95% confidence interval (CI) in RevMan 2012 using a fixed-effect model. We calculated the number needed to treat to benefit (NNTB) and the number needed to treat to harm (NNTH) using the RD and its CI when RDs were significant (Cates 2003).

We recoded polytomous outcome variables as dichotomous variables to enable assessment. For example, an outcome assessed as 'very good, good, poor, no improvement' was recoded as 'actual improvement versus poor or no improvement'.

Unit of analysis issues

We took into account differences in populations, inclusion and exclusion criteria, interventions and outcome assessment, and we undertook a qualitative comparison of the studies to determine if pooling of the results was reasonable. We chose primary endpoints as the proportion of participants presenting a relevant symptom at a common date.

Dealing with missing data

We were not able to contact the original investigators to request missing data because the studies were performed more than 22

years ago (median = 36.5 years). There were no missing data for two-thirds of studies. For the remaining third, we analysed only the available data (i.e. ignoring the missing data).

Assessment of heterogeneity

We carried out an assessment of possible heterogeneity (the studies did not evaluate the same effect) for pooled effects using a Breslow-Day test of heterogeneity. We used the I^2 statistic to describe the percentage of total variation across studies that is due to heterogeneity rather than chance (Higgins 2003). A value above 50% may be considered substantial heterogeneity. In case of heterogeneity, we performed an analysis using a random-effects model.

Assessment of reporting biases

Given the number of studies for each comparison (mostly less than four), we did not perform visual and statistical tests for funnel plot asymmetry (RevMan 2012). For the single comparison including the results of four studies, we used visual interpretation (RevMan 2012).

Data synthesis

We used meta-analysis because the systematic review identified several eligible studies with small sample size but with closed designs. We used a random-effects model for meta-analysis when studies were combined to evaluate similar (but not exactly the same) endpoints. Otherwise, we used a fixed-effect model.

Subgroup analysis and investigation of heterogeneity

We performed a subgroup analysis of infants younger than two years of age because of different pharmacokinetics and pharmacodynamics in this age group, as recommended by the topic E 11 ("Clinical investigation of medicinal products in the paediatric population") of the International Conference on Harmonisation (EMEA 2001).

Sensitivity analysis

We did not judge sensitivity analysis to be pertinent given the number of studies for each comparison (mostly less than four).

RESULTS

Description of studies

Results of the search

In July 2010 we searched CENTRAL 2010, Issue 2 and identified 165 references, but found only one potentially relevant study (Zuppi 1984). We searched MEDLINE from 1966 to June 2010 and retrieved 294 references, including 18 potentially relevant studies (Baldini 1989; Banovcin 1992; Bellomo 1967a; Bellomo 1967b; Berni 1983; Biscatti 1972; Boner 1984; Castello 1979; Chalumeau 2002; Henocq 1985; Loscialpo Ramundo 1968; Mayaud 1980; Plietz 1976; Ribeiro 1980; Santangelo 1985; Trastotenojo 1984; Varricchio 2008; Volkl 1992). We searched EMBASE from 1980 to 2010 and identified 425 references, including 12 potentially relevant studies (Baldini 1989; Banovcin 1992; Camurri 1990; Gusberti 1985; Henocq 1985; Malka 1990; Michael 1986; Nikolic 1980; Rudnik 1980; Santangelo 1985; Szekely 1980; Volkl 1992). We searched Micromedex for acetylcysteine and carbocysteine in 2010 and identified three potentially relevant studies (Malka 1990; Ramenghi 1984; Santangelo 1985). We searched Pascal from 1987 to 2004 and identified 101 references, including one potentially relevant study (Malka 1990). From 2005 onwards we no longer had access to Pascal. We searched Science Citation Index from 1974 to June 2010 and identified 162 references, including four potentially relevant studies (Nikolic 1980; Rudnik 1980; Santangelo 1985; Szekely 1980).

We updated the electronic database searches in March 2013 but did not identify any new studies.

We identified the other potentially relevant studies using the references of relevant and non-relevant trials and the request for unpublished trials to drug companies that manufacture acetylcysteine or carbocysteine in France, The Netherlands and the United States, and from authors of relevant and non-relevant studies (Amir 1985; Anonymous 1987; Banovcin 1990; Bellomo 1972; Bellomo 1973; Berger 1978; Caramia 1984; Careddu 1989; Dano 1971; Egreteau 1992; Fiocchi 1989; Gaudier 1968; Ginocchi 1978; Hofmann 1980; Jean 1982; Leupold 1970; Nakayama 1977; Nigam 1981; Olivieri 1979; Poder 1982; Samsygina 1995; Zanini 1974; Zens 1967).

In summary, we included 50 potentially relevant studies to evaluate the efficacy and safety of acetylcysteine and carbocysteine.

Included studies

Studies included to evaluate efficacy

We excluded most of the 50 potentially relevant studies from the efficacy analysis for one or more reason(s) (see Characteristics of excluded studies table). Six trials fulfilled the inclusion criteria and none of the exclusion criteria (Bellomo 1972; Biscatti 1972; Fiocchi 1989; Malka 1990; Nakayama 1977; Zanini 1974) and were eligible to study efficacy (see Characteristics of included studies table).

Four of these six trials were written in French and two in Italian. All six studies were performed more than 17 years ago (median = 32 years). Mucolytics were administrated orally in the six studies.

Studies included to evaluate safety

We excluded sixteen studies from the safety analysis because they mainly involved participants with chronic diseases (Amir 1985; Berger 1978; Egreteau 1992; Hofmann 1980; Nigam 1981; Olivieri 1979; Plietz 1976; Poder 1982; Ribeiro 1980; Rudnik 1980; Samsygina 1995; Szekely 1980; Volkl 1992; Zens 1967; Zuppi 1984) or received additional antibiotic treatments only in the treatment group (Varricchio 2008) (see Characteristics of excluded studies table).

Twenty-eight studies, in addition to the six trials included to study efficacy, fulfilled the inclusion criteria and none of the exclusion criteria to study safety (Table 1).

Among these 28 studies, 11 were written in Italian (Baldini 1989; Bellomo 1967a; Bellomo 1967b; Bellomo 1973; Berni 1983; Camurri 1990; Careddu 1989; Castello 1979 ; Ginocchi 1978; Gusberti 1985; Loscialpo Ramundo 1968), seven in English (Boner 1984; Caramia 1984; Dano 1971; Nikolic 1980; Ramenghi 1984; Santangelo 1985; Trastotenojo 1984), six in French (Anonymous 1987; Chalumeau 2002; Gaudier 1968; Henocq 1985; Jean 1982; Mayaud 1980), two in German (Leupold 1970; Michael 1986) and two in Slovak (Banovcin 1990; Banovcin 1992). Except for a targeted pharmacovigilance study (Chalumeau 2002), the studies were at least 15 years old (median = 23 years). The route of administration was oral in 16

studies, intramuscular in six, inhaled in four, and both oral and intramuscular in two.

Excluded studies

We excluded 44 studies (see Characteristics of excluded studies) for different reasons: active control treatment, chronic disease, no control group, no placebo, no randomisation and/or type of outcome measures.

Risk of bias in included studies

Because the studies dated mainly from at least 15 to 40 years ago (median = 26 years) we were not successful in obtaining additional trial data.

The risk of bias of the six studies included to evaluate efficacy is mentioned in the 'Risk of bias' table (Figure 1; Figure 2). One study had a 'low risk of bias' for all items except for 'incomplete outcome data' for which we judged the risk of bias as 'high' (Nakayama 1977).

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

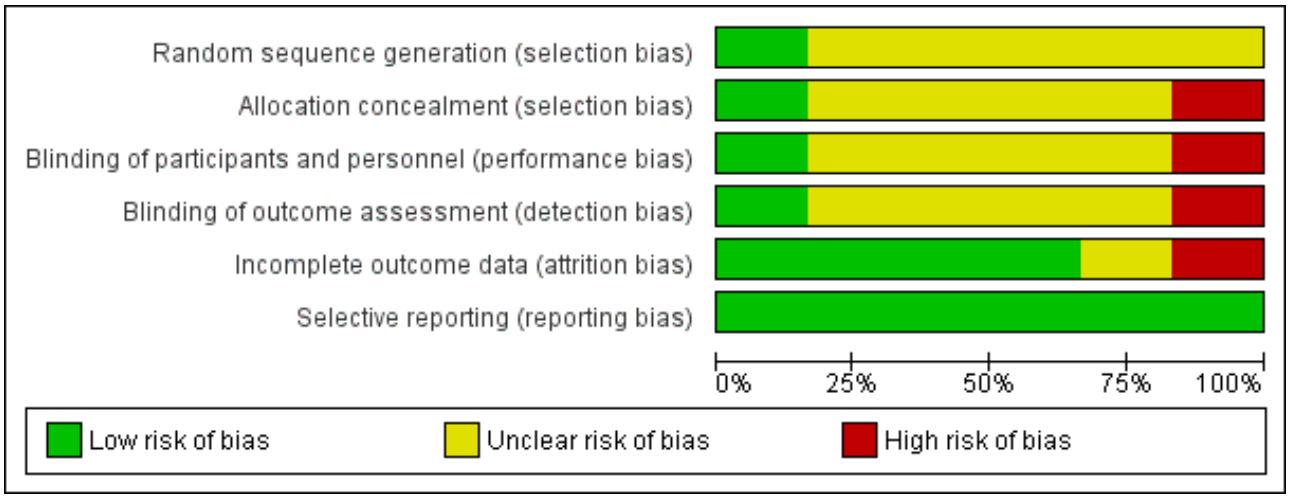
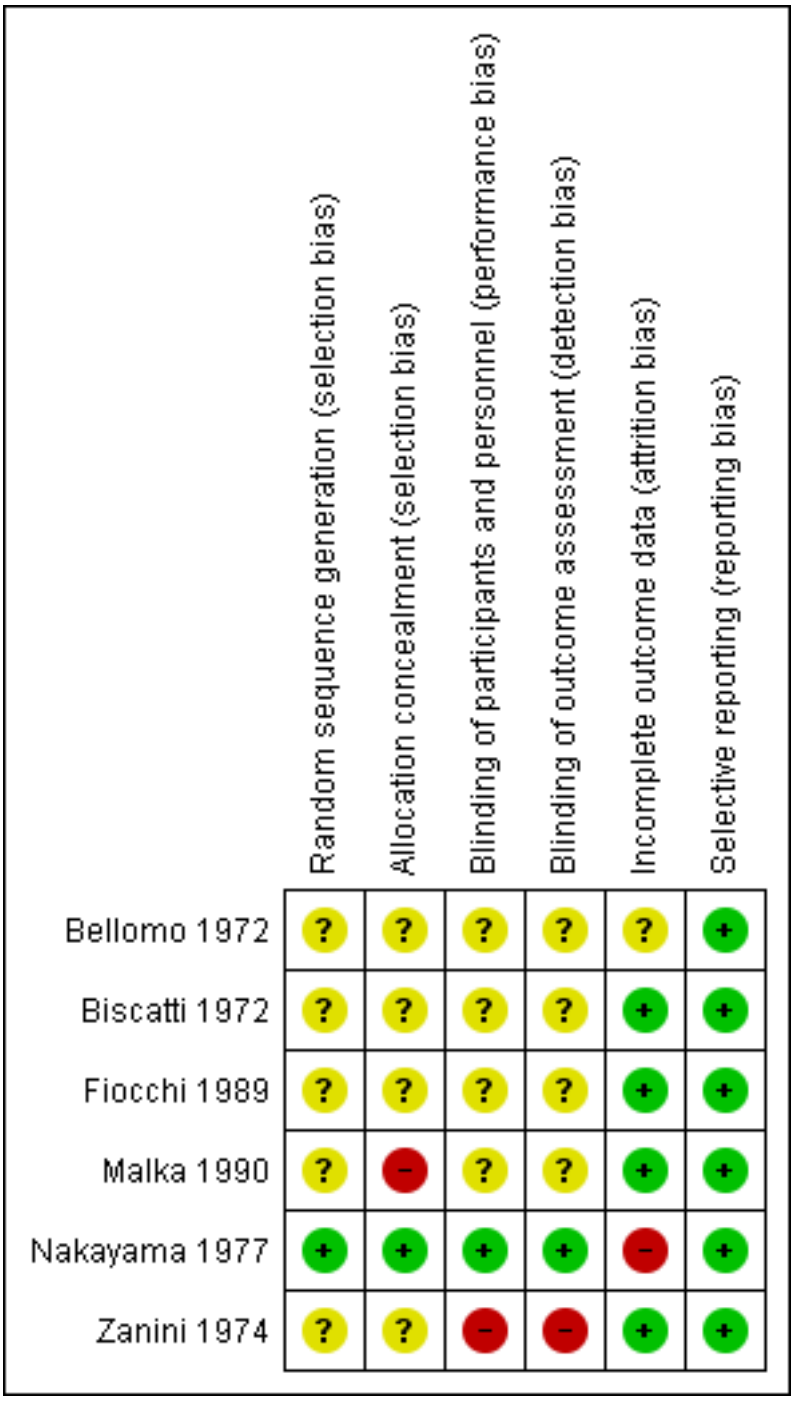


Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Four studies did not report sufficient details on randomisation and allocation concealment to make meaningful conclusions (Bellomo 1972; Biscatti 1972; Fiocchi 1989; Zanini 1974). Only one study had low risk of bias for random sequence generation and allocation concealment (Nakayama 1977). For the last study the investigators did not respect the randomisation list, and therefore we classified it as having a high risk of bias (Malka 1990).

Blinding

Four studies did not report sufficient details on blinding to make meaningful conclusions (Bellomo 1972; Biscatti 1972; Fiocchi 1989; Malka 1990). For one study, we assessed a low risk of bias because all the blinding conditions were clearly mentioned and respected (Nakayama 1977). For the last study, authors "had noticed the better efficacy of one of the products in looking clinically at the therapeutic results" and so we assessed this as a high risk of bias (Zanini 1974).

Incomplete outcome data

In four studies, analyses were based on the data of all included patients, and therefore we assessed them as having a low risk of bias (Biscatti 1972; Fiocchi 1989; Malka 1990; Zanini 1974). For one study, it was mentioned that not all the patients were included in the analysis (Nakayama 1977).

Selective reporting

All studies were considered as having a low risk of reporting bias because they all mentioned relevant outcomes.

Other potential sources of bias

None.

Effects of interventions

1. Efficacy

The six included trials involved 497 participants and compared cysteine derivatives with placebo (Bellomo 1972; Biscatti 1972; Fiocchi 1989; Malka 1990; Nakayama 1977; Zanini 1974).

1.a Analysis of included studies with acetylcysteine

Acetylcysteine was tested in three trials (Bellomo 1972; Biscatti 1972; Fiocchi 1989) with a total of 209 participants. The first study included 59 patients with acute bronchitis or broncho-pulmonary infections and compared oral administration of the antibiotic-mucolytic combination (thiamphenicol glycinate acetylcysteinate) (n_1 = 30) with thiamphenicol alone (n_2 = 29) as an active control at the dose of 14 mg/kg/day of acetylcysteine with a duration of treatment of six days (Bellomo 1972). There was total remission of febrile state, dyspnoea, "thoracic semeiologic alterations" (i.e., "wheezing breathing", rattling) and cough in both groups. However, there was a statistically significant more rapid remission in the group treated with the antibiotic-mucolytic combination. For example, there was total remission of febrile state in the treated group after six days, but it took nine days for the recovery of all the patients in the placebo group (P = 0.03).

The second study included patients with acute upper and lower respiratory tract infections (RTIs) and compared oral administration of acetylcysteine (n_1 = 25) and placebo (n_2 = 25) at a daily dose of 100 to 300 mg of acetylcysteine, depending on age, for six days (Biscatti 1972). All participants received some kind of antibiotic. The clinical parameters returned to normal in a statistically significant shorter time in the acetylcysteine group. For example, by the end of the treatment (six days), the remission of cough was total in the treated group whereas the cough persisted in 16% of the participants in the placebo group (risk difference (RD) -16%, 95% confidence interval (CI) -31% to -1%), risk ratio (RR) 0.11 (95% CI 0.01 to 1.95).

The third study compared oral acetylcysteine (n_1 = 50) with placebo (n_2 = 50) at a daily dose of 20 mg/kg, subdivided into three daily administrations for 28 days in children with bronchitis or tracheitis (Fiocchi 1989). Participants received antibiotics if necessary. Clinical improvement was observed in the four groups by the end of the trial. In the subgroup of children with bronchitis, statistically significant differences in the clinical parameters (cough score, cough productivity and thoracic semeiologic alterations) were recorded favourably for the acetylcysteine treatment. For example, the median cough score (range = 0 to 3) decreased faster in the treated group with a difference before/after of 2.1 (2.20 to 0.10), whereas in the placebo group the median score dropped from 2.20 to 0.50 (P < 0.05).

In the subgroup of children with tracheitis, no statistically significant differences were noted on the various clinical parameters, except a statistically significant improvement of the cough score, with a difference before/after of 2.00 (2.10 to 0.10) in the acetylcysteine treatment subgroup and 1.60 (2.10 to 0.50) in the placebo group (P < 0.05). We performed a comparison of the two groups (Analysis 2.3; Analysis 2.4; Analysis 4.4; Analysis 4.5; Analysis 6.1; Analysis 6.2): the treatment reduced the risk of "thoracic semeiologic alterations" by 83% (RR 0.17, 95% CI 0.03 to 0.99) (Analysis 4.5) and the RD at the end of the treatment was statistically significant: RD -14% (-25% to -3%). The number needed to treat to benefit (NNTB) was eight (4 to 34). Regarding cough, the RD was -3% (-13% to 7%) and the RR 0.67 (95% CI 0.16 to 2.76) (Analysis 2.4). At the end of the trial, productive cough was still present in three participants treated with acetylcysteine versus seven patients in the placebo group. The RD was not statistically significant though: RD -8% (-20% to 3%) and the RR 0.41 (95% CI 0.11 to 1.56).

1.b Analysis of included studies with carbocysteine

Carbocysteine was tested in three of the six included studies (Malka 1990; Nakayama 1977; Zanini 1974) with a total of 288 participants. The first study included 106 participants with acute bronchitis, and compared oral administration of carbocysteine (n_1 = 49) with placebo (n_2 = 57) at a dose of 200 to 300 mg/day, depending on age, for seven days (Malka 1990). Both groups received antibiotics if necessary. The clinical symptoms (cough, expectoration, bronchial congestion, dyspnoea) and pulmonary function test abnormalities diminished in both groups. Significant differences between the two groups were observed for expectoration and pulmonary function tests. For example, after four days, expectoration was easier for 69% of the treated participants versus 49% of the participants of the placebo group (RD 23% (1% to 47%)).

The second study included 152 participants with respiratory diseases (bronchial asthma or acute bronchitis) and compared oral administration of carbocysteine (n_1 = 74) with placebo (n_2 = 78) at a dose of 30 mg/kg/day, three to four times daily for seven days (Nakayama 1977). Both groups received bronchodilators, antibiotics and antihistamines if previously treated. The author reported improvement in clinical symptoms in both groups: global impression, cough, stridor, expectoration. The difference in improvement for overall assessment, stridor and expectoration was statistically significant in favour of the treatment group, but the data were available only for the outcome "overall assessment". The analysis of these data showed a RD of 17% (3% to 31%) and a NNTB of six (4 to 32).

The third study included 30 participants with respiratory infections (such as bronchitis) and compared oral administration of carbocysteine (n_1 = 19) with placebo (n_2 = 11) at a dose of 100 to 400 mg/day according to age for five to nine days (Zanini 1974) in participants hospitalised for acute respiratory infections. Participants in both groups received antibiotics if necessary. Improvement of clinical signs (cough, vomiting/dyspnoea, temperature, appetite, general condition) was observed

in both groups, with significant improvement for cough, vomiting and dyspnoea in both groups, but the actual improvement of general condition was better in the placebo group. Though not significant, the RD was 12% (-24% to 49%) in favour of the placebo group.

1.c Pooled analysis

Because we could include very few studies, we have pooled the results of trials involving acetylcysteine and/or carbocysteine. We also considered primary endpoints that were similar but not exactly the same, for example, when the endpoint had close but slightly different dates. As a consequence, we used random-effects models when both acetylcysteine and carbocysteine were involved and/or when the primary endpoints were not exactly the same.

Five major endpoints could be considered for meta-analysis: febrile state after six days (Analysis 1.1; Analysis 1.2), cough after six to seven days (Analysis 2.1; Analysis 2.2), dyspnoea after six to seven days (Analysis 3.1; Analysis 3.2), thoracic semeiologic alterations after five days (Analysis 4.1; Analysis 4.2; Analysis 4.3) and general condition after six to seven days (Analysis 5.1; Analysis 5.2).

We calculated pooled RDs and when possible, pooled RRs to assess these outcomes. Febrile state after six days and cough after six to seven days were evaluated in three trials (Bellomo 1972; Biscatti 1972; Zanini 1974). The first two studies involved acetylcysteine and the last one, carbocysteine, and the outcome was not considered at exactly the same date (after six days or after an average of six days), so we used a random-effects model. After six days, three participants were still febrile among the participants from the placebo group, whereas none presented fever in the treated group: the pooled RD was -5% (-12% to 2%) (Figure 3). Then, the RR was 0.21 (95% CI 0.02 to 1.77). Regarding cough, after six to seven days of treatment, the risk difference was -10% (-19% to -1%) (Figure 4) and the NNTB was 10 (6 to 101). The RR was 0.37 (95% CI 0.12 to 1.20).

Figure 3. Forest plot of comparison: 1 Febrile state (AC vs placebo), outcome: 1.1 Febrile state after 6 days.

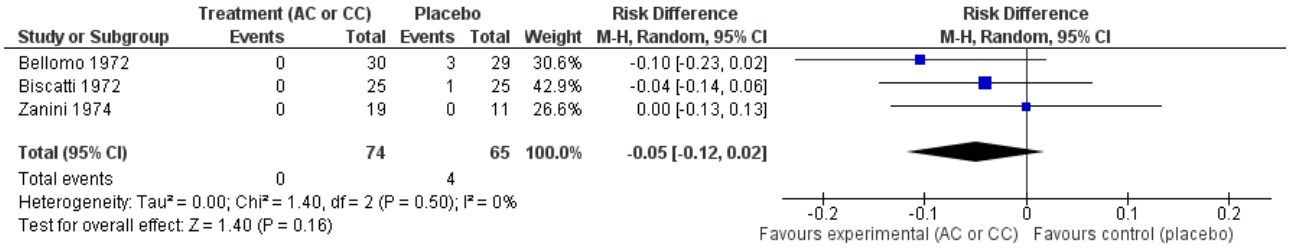
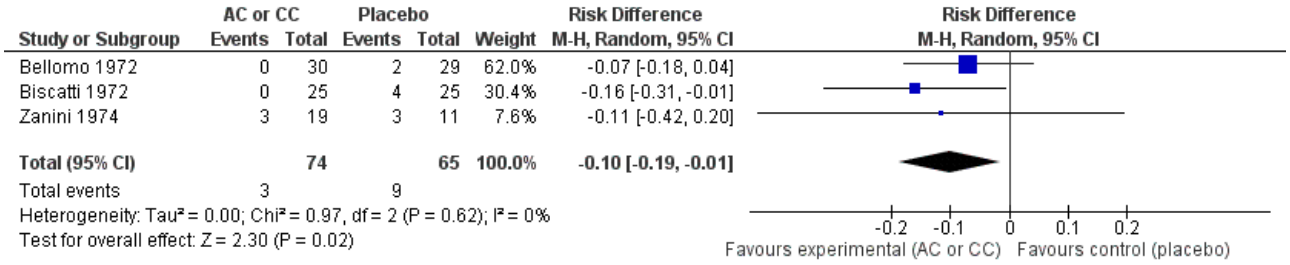
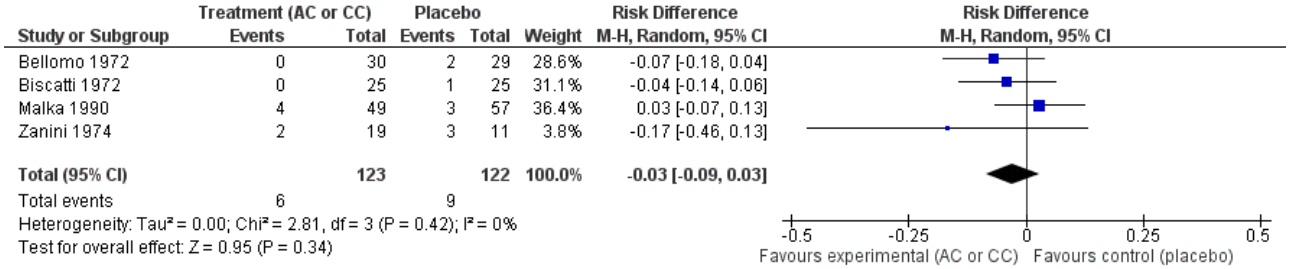


Figure 4. Forest plot of comparison: 4 Cough (AC vs placebo), outcome: 4.1 Cough after 6 to 7 days.



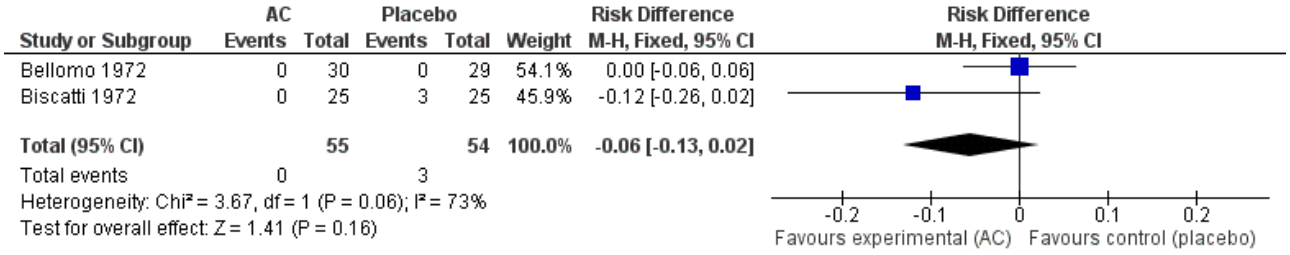
The assessment of the efficacy of acetylcysteine and carbocysteine to treat dyspnoea involved an additional trial (Malka 1990). Six participants treated complained of dyspnoea after six to seven days versus nine in the placebo group. The RD was -3% (-9% to 3%) (Figure 5) and the RR was 0.66 (95% CI 0.25 to 1.74).

Figure 5. Forest plot of comparison: 3 Dyspnoea (AC or CC versus placebo), outcome: 3.1 Dyspnoea after 6 to 7 days.



We pooled data from two studies to evaluate the efficacy of acetylcysteine in the treatment of thoracic semeiologic alterations (Bellomo 1972; Biscatti 1972). After three days, no treated participant was presenting that symptom versus three in the placebo group; the RD was 6% (-13% to 2%) (Figure 6). However, there was heterogeneity between the studies. After using a random-effects model the RD was -5% (-20% to 10%).

Figure 6. Forest plot of comparison: 3 Thoracic semeiologic alterations (AC vs placebo), outcome: 3.1 Thoracic semeiologic alterations (after 3 days).



We also assessed the efficacy on the general condition using the data from two studies involving carbocysteine (Nakayama 1977; Zanini 1974). After seven days, 24 children were still presenting a deteriorated general condition in the treatment group and 32 in the placebo group. The RD was -7% (-35% to 20%) and the RR was 0.78 (95% CI 0.31 to 1.95).

1.d Subgroup analysis of infants under two years

Among the studies with acetylcysteine, Bellomo 1972 studied 22 children under one year of age and 28 children between one and five years of age, and Biscatti 1972 studied 29 children under two years of age. However, it was not possible to obtain more information about possible differences in results in the different age groups.

Among the studies with carbocysteine, Nakayama 1977 studied children from one to 14 years old and Zanini 1974 studied 18 children under one year of age. However, it was not possible to obtain more information about possible differences in results in the children under two years of age.

2. Safety

Our search strategy identified 28 studies to evaluate safety, in addition to the six trials above (Bellomo 1972; Biscatti 1972; Fiocchi 1989; Malka 1990; Nakayama 1977; Zanini 1974). These 34 studies involved 2064 paediatric participants. Safety was evaluated using clinical, biological, radiographic or pulmonary function test parameters. Among these studies, 17 were controlled trials (including 14 randomised controlled trials (RCTs)), 16 were non-controlled trials and the last one was a targeted pharmacovigilance study. The studies reporting adverse events were not comparable in terms of participants, interventions or adverse events, and so we judged pooling of the results to be inappropriate.

2.a Analysis of included studies with acetylcysteine

Twenty studies evaluated acetylcysteine, involving 1080 participants among which 831 were treated (Baldini 1989; Bellomo 1967a; Bellomo 1967b; Bellomo 1972; Bellomo 1973; Biscatti 1972; Boner 1984; Camurri 1990; Caramia 1984; Dano 1971; Fiocchi 1989; Gusberti 1985; Jean 1982; Leupold 1970; Loscialpo Ramundo 1968; Mayaud 1980; Nikolic 1980; Ramenghi 1984; Santangelo 1985; Trastotenojo 1984).

Nine of these studies were controlled trials in which the treatment was administered orally except in one study for which the route of administration was intramuscular. Control participants received either placebo (Bellomo 1972; Biscatti 1972; Fiocchi 1989; Trastotenojo 1984), an active control treatment (Baldini 1989; Camurri 1990; Gusberti 1985) or nothing (Bellomo 1967a). If a concomitant treatment was authorised, for example, antibiotics, it was authorised for all participants. The controlled trials studied clinical or biological tolerance, or both. The biological tests consisted usually of full blood tests (haemoglobin (Hb), red blood count (RBC), white blood count (WBC) and platelets) and the monitoring of hepatic (bilirubin, serum glutamate-oxaloacetate transaminase (SGOT), serum glutamate-pyruvate transaminase (SGPT), alkaline phosphatase) and renal function (creatinine). In two studies, safety was also evaluated using radiographic (Trastotenojo 1984) or pulmonary function test parameters (Fiocchi 1989). The controlled trials all showed good clinical safety, except mild gastrointestinal tract adverse events (vomiting) in two participants (2%), leading to the withdrawal of one of them (Fiocchi 1989).

In the other trials, the route of administration was oral in one study, intramuscular in five, inhaled in four, and both oral and intramuscular in one. Most of these studies authorised concomitant treatments, mainly antibiotics. All participants had equal access to these treatments, except in one trial (Zanini 1974). Safety was evaluated using clinical and typically biological tests. Some studies also evaluated safety using radiographic (Boner 1984; Caramia 1984; Jean 1982; Loscialpo Ramundo 1968; Mayaud 1980; Santangelo 1985) or pulmonary function test parameters (Dano 1971; Leupold 1970). In one study, the tolerance was not documented (Nikolic 1980). The main potential adverse event observed was broncho-constriction induced by inhaled N-acetylcysteine in children older than two years of age (Dano 1971; Leupold 1970). As a consequence, 11 children (31%) were withdrawn from one of these studies (Leupold 1970). This side effect was mainly explained by the trial authors by the high concentration (20%) of acetylcysteine. Whereas in another study, no such effect was reported with a lower concentration (10%) (Loscialpo Ramundo 1968). In the other uncontrolled trials clinical safety was very good except in one study where 12 participants (11%) complained of gastro-intestinal tract disorders (nausea, vomiting, diarrhoea), but none were withdrawn (Mayaud 1980).

2.b Analysis of included studies with carbocysteine

Thirteen studies evaluated carbocysteine, involving 989 participants, among which 755 were treated (Anonymous 1987; Banovcin 1990; Banovcin 1992; Berni 1983; Careddu 1989; Castello 1979; Gaudier 1968; Ginocchi 1978; Henocq 1985; Malka 1990; Michael 1986; Nakayama 1977; Zanini 1974).

The treatment was administrated orally. Eight trials were controlled. The control participants received either a placebo (Malka 1990; Nakayama 1977; Zanini 1974), or an active treatment (Banovcin 1990; Banovcin 1992; Berni 1983; Careddu 1989) or nothing (Henocq 1985). If a concomitant treatment was authorised, for example, antibiotics, it was authorised for all participants. The controlled trials used clinical and sometimes biological parameters to evaluate safety. The biological tests consisted of blood tests and/or the monitoring of hepatic and renal function. In two studies, safety was also evaluated using pulmonary function test parameters (Malka 1990; Nakayama 1977). Three studies did not document adverse events (Banovcin 1990; Banovcin 1992; Henocq 1985). The overall clinical safety was good in the other trials, with few participants (n = 19; 13%) complaining of gastrointestinal tract disorders (nausea, vomiting, diarrhoea) (Careddu 1989; Malka 1990), leading to the withdrawal or dropping out of two (1.9%) treated children and one (0.9%) among the control patients (Malka 1990). In one of these two studies (Careddu 1989) the dose used was high (900 mg/day for children weighing around 25 kg).

The other studies involved 501 paediatric participants. One study authorised antibiotics for all participants if necessary (Castello 1979) and another one authorised antibiotics in 33 children (75%) (Ginocchi 1978). All trials studied clinical tolerance. Biological parameters (Ginocchi 1978) and sputum viscosimetry (Castello 1979) were also used in two trials. Adverse events were observed in 13 participants (2.6%). These participants experienced gastrointestinal tract disorders (stomach pain, nausea, vomiting, diarrhoea) in two studies (Gaudier 1968; Michael 1986), leading to the withdrawal of five participants (1.3%) in one study (Michael 1986).

Our search identified only one study designed to evaluate safety (Anonymous 1987). This study was an open uncontrolled trial that involved 20 participants with acute upper and lower RTIs, including some infants. Participants received carbocysteine for six days at a dose of 200 mg per day via the oral route. No concomitant treatment was allowed, except antibiotics in one child. The safety was evaluated clinically by questioning parents and children. The only potentially adverse event reported (vomiting) occurred after the end of the treatment and involved only the child on antibiotics.

2.c Subgroup analysis of infants under two years of age

Among the 22 studies that provided clear data on participants' ages, only 10 included participants under two years, involving 262 patients (68%) under this age (Banovcin 1992; Bellomo 1967a; Bellomo 1967b; Bellomo 1973; Biscatti 1972; Castello 1979; Chalumeau 2002; Ginocchi 1978; Jean 1982; Ramenghi 1984). Among the 10 studies, only one was a good-quality controlled trial (Biscatti 1972) and three were low-quality controlled trials (Banovcin 1992; Bellomo 1967a; Bellomo 1973). One hundred and seventy-four participants (75%) under two years of age were included in these four trials; 26 were treated with carbocysteine (Banovcin 1992) and 59 with acetylcysteine, including 14 in the single good-quality controlled trial (Biscatti 1972). None of them had side effects. No side effect was reported in the other six trials.

Our search strategy also identified a targeted pharmacovigilance study (Chalumeau 2002). This study followed the spontaneous reporting to the French pharmacovigilance system of cases of paradoxically increased bronchorrhoea in infants receiving mucolytic agents. This prospective two-month study was performed in the emergency departments of two paediatric teaching hospitals in Paris, France. During this period, six participants were diagnosed as having a paradoxically increased bronchorrhoea after having received acetylcysteine (n = 3) or carbocysteine (n = 3) for acute upper and lower respiratory infections. Participants were aged 2.5 to 7.5 months old. The median delay between treatment and the diagnosis of paradoxically increased bronchorrhoea was 4.5 days. The dose was on average 26 mg/kg/day, ranging from 20 to 35 mg/kg/day. Two children were hospitalised because of their respiratory state. Using the Naranjo scale for causality assessment, the causality between the exposure and the adverse reaction was considered possible or plausible (Naranjo 1981).

DISCUSSION

Summary of main results

We found a limited number of studies that evaluated the efficacy of acetylcysteine and carbocysteine as symptomatic treatments for acute upper and lower respiratory tract infections (RTIs) in paediatric patients without chronic broncho-pulmonary disease (Bellomo 1972; Biscatti 1972; Fiocchi 1989; Malka 1990; Nakayama 1977; Zanini 1974). These trials showed some benefit from mucolytic agents, although differences were sometimes small, not statistically significant and/or of little clinical relevance. Considering the pooling of data, the effect of acetylcysteine or carbocysteine was not statistically significant except for cough after six to seven days. The treatment (acetylcysteine or carbocysteine) reduced the risk of cough by 63%. However, the number needed to treat to benefit (NNTB) was 10 with a large CI (6 to 101), suggesting a questionable effect size. Only one of the six trials was considered to have a low risk of bias (Nakayama 1977; Figure 2). However, in the low risk of bias trial by Nakayama 1977, an overall criterion based on an improvement in global condition was used as an outcome, but this composite criterion has not been validated and may not be clinically relevant. No statistically significant difference was observed regarding most symptoms considered separately, especially expectoration and cough. It was not possible to make any evaluation about the subgroup of infants under two years of age, because none of the six studies that we included to evaluate efficacy mentioned the results for this age group separately.

The overall safety of acetylcysteine and carbocysteine was good, with mainly minor gastrointestinal tract disorders in few participants (n = 46; 2%). These findings should not lead to the conclusion that mucolytic agents are well tolerated in paediatric patients. In fact, (i) the size of the low risk of bias trial was not sufficient to provide enough statistical power to detect any rare potentially severe adverse event, (ii) many high risk of bias trials did not provide detailed descriptions of the severity of adverse events and abnormal laboratory tests or reasons for treatment discontinuation separately for each intervention group, and (iii) very few children under two years of age were involved in the studies. RCTs of adequate sample size offer the only unbiased

approach for assessing the frequency and severity of side effects from a given medication, but when that kind of evidence is lacking, other sources, such as pharmacovigilance and pharmaco-epidemiology can be helpful.

Regarding the safety of mucolytic agents in paediatric patients, attention should be paid to the youngest age group. In a targeted prospective pharmacovigilance study in two paediatric emergency departments, six infants (all younger than eight months old) were diagnosed with paradoxically increased bronchorrhoea during a two-month period (Chalumeau 2002). An analysis of the French pharmacovigilance system concerning adverse drug reactions to acetylcysteine and carbocysteine showed 59 respiratory adverse drug reactions in children younger than six years from 1989 to 2008 (30 children received carbocysteine, 28 received acetylcysteine and one child received both drugs at the same time). The respiratory adverse drug reactions reported were increased and/or prolonged cough, increased bronchorrhoea, worsening of respiratory distress, mucous vomiting and dyspnoea (Mallet 2011). Fifty-one children (86%) required hospitalisation or extended hospitalisation because of the adverse drug reactions. Outcome was favourable in all cases except for one patient in whom pleuropneumonia developed and a one-year-old girl who died of pulmonary oedema that was considered secondary to mucous vomiting according to the reporting physician. These side effects led to the withdrawal of the licence for carbocysteine and acetylcysteine in paediatric patients younger than two years of age in France and Italy in April 2010 (Mourdi 2010).

This paradoxical reaction was also mentioned but not documented with references in some articles (Harris 1967; Jean 1982) and textbooks (Anonymous 2000a; Anonymous 2000b). The paradoxically increased bronchorrhoea could be explained by the effective action of mucolytic agents which increase bronchial mucous flow. This flow may exceed the capacity of spontaneous drainage of the infant which is limited by the small bronchial diameter and neuromuscular physiologic immaturity (Wohl 1998). This could also be explained by a dose-related effect. No dose-response trial has ever been performed for acetylcysteine, leading to a unique dose recommendation of 200 mg per day, whatever the weight of the child. According to the World Health Organization (WHO) standards (WHO 2007), the median weight of a one-month-old infant is about 4.5 kg as opposed to 12.2 kg for a two-year-old. The recommended dose for the youngest infants is then three times higher than the dose recommended for the oldest (about 45 mg/kg/day versus 16 mg/kg/day). This may lead to dose-related adverse events in very young infants. In the same way, no clinical research has been implemented to support the recommended dose of the marketing authorisation of carbocysteine (200 to 300 mg/day). The evaluation of drug safety should depend on age, considering that pharmacokinetics and pharmacodynamics in paediatric patients differ greatly from adults, especially in neonates and infants. Paradoxical side effects are not rare in these age groups (Hughes 1994) but a causal relationship is difficult to prove when a paradoxical side effect of a drug is suspected because of protopathic bias. The term *protopathic bias* is used if the first symptoms of the outcome of interest are the reasons for use of treatment (Salas 1999). This bias leads people to believe that when symptoms worsen during the course of a drug that is prescribed for a specific disease it may be related to the disease itself and not to the drug (Delgado-Rodriguez 2004; Horwitz 1980). The only way to evaluate paradoxical side effects of drugs avoiding protopathic bias would be theoretically to study them in another unrelated disease. However, this is not possible in the case of carbocysteine because its only indications are RTIs. For acetylcysteine, in a multicentre, post-marketing safety study, respiratory symptoms were reported in 2.2% of paediatric (n = 1905) patients receiving intravenous acetylcysteine for acetaminophen overdose between 1980 and 2005. Respiratory symptoms included bronchospasm, cough, wheezing, stridor, shortness of breath, chest tightness or respiratory distress (Cumberland Pharmaceuticals 2008).

Overall completeness and applicability of evidence

The external validity of this review is difficult to evaluate. On the one hand, it seems high given the various settings of the studies, the various types of participants, the various type of interventions and outcomes. On the other hand, the meaning of results observed in studies performed 40 years ago in patients with clinical conditions and general management that are very different from the current practices is questionable.

The evaluation of the benefit-risk ratio of mucolytic agents should take into consideration the fact that these medicines are prescribed for self limiting diseases (for example, acute cough, bronchitis). For example, in the Bellomo 1972 study, remission for all symptoms was complete in the placebo group within nine days at most. Regarding paediatric patients older than two years, no serious adverse events were reported in the available studies included in the present review. These studies suggest that acetylcysteine and carbocysteine may reduce frequency, intensity and duration of symptoms in acute upper and lower RTIs. For the patient group younger than two years, the benefit-risk ratio is most probably negative according to available evidence for side effects in this age group.

Our review has some implications for drug regulation agencies. Acetylcysteine and carbocysteine are licensed for use for the treatment of acute upper and lower RTIs in paediatric patients in many European countries. According to our review, this license is not supported by strong evidence in children older than two years of age and is not supported by any evidence in children under two years of age, considering some important concerns about safety (Mallet 2011; Mourdi 2010). A re-evaluation of the benefit-risk ratio of these drugs by the drug regulation agencies of the countries where they are licensed is necessary, particularly in the age group younger than two years.

Quality of the evidence

The body of evidence identified allows a robust conclusion regarding patients younger than two years old. Indeed no study supports the use of acetylcysteine nor carbocysteine among this age group. For children older than two years, our conclusions are based on a small number of studies and patients, with an overall high risk of bias. Thus, the conclusions should be interpreted cautiously.

Potential biases in the review process

Given the effort that was made to contact all drug companies that manufacture acetylcysteine and carbocysteine, the high response rate obtained during this process (as shown by the numerous unpublished studies included) and the various contacts, we are confident that we analysed all relevant data in this review.

Agreements and disagreements with other studies or reviews

Our conclusions are in complete agreement with clinical practice guidelines for the management of cough in children (Chang 2006; Shields 2008) and another systematic review (Smith 2012).

AUTHORS' CONCLUSIONS

Implications for practice

The results of the present review have to be interpreted with caution because (i) it was based on a limited number of patients included in studies whose methodological quality was questionable, and which dated mainly from the 1970s and 1980s, (ii) these results should take into consideration the fact that acetylcysteine and carbocysteine are prescribed for self limiting diseases (for example, acute cough, bronchitis), and (iii) millions of paediatric patients are exposed to these drugs each year in many European countries (Cano Garcinuño 2013; Cazzato 2001; Chalumeau 2000; Collet 1991; Duijvestijn 1997; Horen 2002; Sanz 1988; Sen 2011). These mucolytic agents seem to have some benefits on frequency, intensity and duration of symptoms, and appear to be safe in children older than two years. Regarding children younger than two years old, there are current strong concerns about the safety of acetylcysteine and carbocysteine (Mallet 2011). These concerns led to the withdrawal of their licence in this age group in France and Italy in 2010 (Mourdi 2010). Therefore, these drugs should only be used for acute respiratory tract infections in neonates and infants in the context of a randomised controlled trial.

Implications for research

An adequately powered, randomised, double-blind, placebo-controlled trial evaluating the efficacy and safety of acetylcysteine or carbocysteine should be performed in patients under two years of age. This trial should use a main outcome which is clinically relevant (for example, cough frequency, intensity and duration).

ACKNOWLEDGEMENTS

To Thibault Andrieu (TA) for valuable help in updating the review. To Nadjette Mourdi and John Smucny for their important contributions to the first version of this review. To Gérard Bréart, INSERM U953, and Gérard Pons, Paris Descartes University, for their valuable advice on the protocol, the analyses and the manuscript (Paris, France). To Liz Dooley, Cochrane Acute Respiratory Infections Group Managing Editor, for her very comprehensive editorial work. To Ruth Foxlee and Sarah Thorning, for their help with the electronic searches. To Bernard and France Drujon-d'Astros (Aix-en-Provence, France), Barbara Duijvestijn (Heiloo, The Netherlands) and Grace Tjebbes (Heiloo, The Netherlands), for their help with translations from German, Italian and Russian. To Dr Françoise Bavoux and Dr Caroline Pecriaux, Regional Center for Pharmacovigilance and Information on Drugs, Paris, France. Finally, the review authors wish to thank the following people for commenting on drafts of this review: Anne Lyddiatt, Linda Hornbeek, Ann Fonfa, Inge Axelsson, Bruce Arroll, Teresa Neeman, Conor Teljeur and Jenny Doust.

REFERENCES

References to studies included in this review

Bellomo 1972 *{published data only}*

Bellomo G, Giudice S. Controlled study on the efficacy of a combination "thiamphenicol-acetylcysteine" in oral administration in respiratory infections in pediatrics [Studio controllata sull'efficacia della combinazione "tiamfenicolo-acetilcisteina" per via orale nel trattamento delle infezioni broncopolmonari dell'infanzia]. *Clinical Pediatrics* 1972;**54**:30-51.

Biscatti 1972 *{published data only}*

Biscatti G, Bruschelli M, Damonte G, Capozzi F. Controlled studies of the clinical effects of acetylcysteine in oral administration in respiratory infections in pediatrics [Ricerca controllata sugli effetti clinici dell'acetilcisteina per via orale nelle infezioni respiratorie in pediatria]. *Minerva Pediatrica* 1972;**24**:1075-84.

Fiocchi 1989 *{published data only}*

Fiocchi A, Vignati B, Sala M, Arancio R, Banderali G, Marangione P, et al. A new n-acetylcysteine formulation in acute bronchopneumopathy in children [La n-acetilcisteina nel trattamento delle broncopneumopatie acute in pediatria]. *Giornale Italiano delle Malattie del Torace* 1989;**43**:327-34.

Malka 1990 *{published data only}*

Malka M, Lablache Combier B. Carbocysteine in the treatment of acute bronchitis in children [Interet d'un mucolytique, la carbocistéine, dans la bronchite aiguë de l'enfant]. *Medicina Infantil* 1990;**97**:687-92.

Nakayama 1977 *{published data only}*

Nakayama Y, Maeda K, Fuanabashi S, Kubagawa T, Simanugi K, Tateno K, et al. Carbocysteine syrup in pediatrics: a clinical trial [Effets cliniques de s-carboxymethylcysteine sous forme de sirop en pédiatrie (traduction)]. *Japanese Journal of Pediatrics* 1977;**10**:1823.

Zanini 1974 *{published data only}*

Zanini A, Dodesni G. Lisomucil in pediatrics [Il lisomucil in campo pediatrico]. *Clinica Europea* 1974;**13**:1-12.

References to studies excluded from this review

Amir 1985 *{published data only}*

Amir J, Wilunsky E, Zelikovic I, Reisner SH. Acetylcysteine for severe atelectasis in premature infants. *Clinical Pharmacy* 1985;**4**:255.

Anonymous 1987 *{unpublished data only}*

Anonymous. A study of tolerance of carbocisteine syrup in children [Etude de la tolérance clinique du sirop carbocistéine chez l'enfant]. Dossier d'autorisation de mise sur le marché, Laboratoires Alpharma, Aubervilliers, France 1987.

Baldini 1989 *{published data only}*

Baldini G, Gucci M, Taro D, Memmini C. Controlled clinical study of a new Ambroxol formula in the treatment of infantile spastic bronchitis [Studio clinico controllato sull'attivita di una nuova formulazione di Ambroxol nella bronchite asmatiforme del bambino]. *Minerva Pediatrica* 1989;**41**:91-5.

Banovcin 1990 *{published data only}*

Banovcin P. Efficacy of carbocysteine in the treatment of bronchopneumonias in children. *Prakticky Lekar* 1990;**70**:885-7.

Banovcin 1992 *{published data only}*

Banovcin P, Jakusova L, Rosslerova V, Miklerova M, Pullman R. Carbocysteine in the treatment of recurrent bronchitis in infants [Karbocystein v liecbe recidivujucich bronchitid u dojciat]. *Ceskoslovenska Pediatrie* 1992;**47**:543-6.

Bellomo 1967a *{published data only}*

Bellomo G, Frigerio G, Tirantello G. Controlled study on the use of intramuscular acetylcysteine in acute respiratory infections in pediatrics [Ricerche controllate sull'impiego dell'acetilcisteina per via intramuscolare nelle infezioni respiratorie acute in pediatria]. *Clinica Terapeutica* 1967;**43**:437-58.

Bellomo 1967b *{published data only}*

Bellomo G, Tirantello G, Giudice S. On the use of a combination of acetylcysteine with thiamphenicol glycinate in the systemic treatment of bronchopulmonary infections in children [Sull'uso di una combinazione dell'acetilcysteina con tiamfenicolo glicato nel trattamento sistemico delle infezioni broncopolmonari in eta' pediatrica]. *Clinical Pediatrics* 1967;**49**:402-24.

Bellomo 1973 *{published data only}*

Bellomo G, Giudice S, Ganci C. Comparative study of the efficacy of acetylcysteine by the oral and intramuscular routes in acute respiratory affections in pediatrics [Studio comparativo dell'efficacia dell'acetilcisteina per via orale ed intramuscolare nelle affezioni respiratorie acute in pediatria]. *Minerva Pediatrica* 1973;**25**:844-9.

Berger 1978 *{published data only}*

Berger von G, Gottschalk B, Leupold W. Initial experiences with ultrasonic aerosol therapy at home in children with bronchiectasis [Erste erfahrungen mit der ultraschall-aerosolbehandlung unter heimbedingungen bei kindern mit bronchiektasen]. *Kinderärztliche Praxis* 1978;**46**:523-7.

Berni 1983 *{published data only}*

Berni M, Collina A, Zavattini G. Ambroxol in bronchopulmonary pathology in children [Ambroxol nella patologia broncopolmonare del bambino]. *Clinica Terapeutica* 1983;**106**:351-5.

Boner 1984 *{published data only}*

Boner AL, Valletta EA, Stocchero L, Richelli C, Bennati D. Combined antibiotic plus mucolytic treatment of acute or recurrent pneumonia in children. *Drugs Under Experimental and Clinical Research* 1984;**10**:627-30.

Camurri 1990 *{published data only}*

Camurri S, Marenco G. Clinical evaluation of the safety and efficacy of a new pharmaceutical formulation of bromhexine compared to N-acetylcysteine in pediatric patients with acute bronchitis [Valutazione clinica dell'efficacia e della tollerabilita della nuova formulazione farmaceutica bromessina granulare nei confronti dell'N-acetilcisteina granulare in piccoli pazienti affetti da bronchite acuta]. *Gazzetta Medica Italiana* 1990;**149**:45-8.

Caramia 1984 *{published data only}*

Caramia G, Bizzarri V, Compagnoni L, Gregorini S. Combined antibiotic plus mucolytic treatment in broncho-pulmonary disease: cefuroxime plus acetylcysteine. *Current Therapeutic Research, Clinical and Experimental* 1984;**36**:658-63.

Careddu 1989 *{published data only}*

Careddu P, Bernocchi D, Scotti L, Manini G, Mezzopane A. Therapeutic activity and tolerability of a new mucoregulating drug called nesosteine in the treatment of acute diseases of the respiratory apparatus. Controlled pediatric study vs carbocysteine [Attivita terapeutica e tollerabilita di un nuovo farmaco mucoregolatore denominato nesosteina nel trattamento di affezioni acute dell'apparato respiratorio studio pediatrico controllato vs carbocisteina]. *Giornale Italiano Delle Malattie Del Torace* 1989;**43**:47-52.

Castello 1979 *{published data only}*

Castello D, Costa G, de Candussio G. Modifications in catarrhal bronchitis secretion in paediatric age following treatment with S-carboxymethyl-cystein (viscosimetric study) [Modificazioni dell'escreato nella bronchite catarrale in eta pediatrica dopo trattamento con S-carbossimetilcisteina (indagine viscosimetrica)]. *Minerva Pediatrica* 1979;**31**:371-80.

Chalumeau 2002 *{published data only}*

Chalumeau M, Cheron G, assathiany R, Moulin F, Bavoux F, Breart G, et al. Mucolytic agents for acute respiratory tract infections in infants: a pharmacoepidemiologic problem? [Fluidifiants bronchiques dans les infections respiratoires aiguës du nourrisson: un problème pharmacoépidémiologique?]. *Archives de Pédiatrie* 2002;**9**:1128-36.

Dano 1971 *{published data only}*

Dano G. Bronchospasm caused by acetylcysteine in children with bronchial asthma. *Acta Allergologica* 1971;**26**:181-90.

Egreteau 1992 *{published data only}*

Egreteau L, Gaillard D, Jouet JB, Plotkowski L, Zahm JM, Pierrot D, et al. Effect of carbocisteine on mucus and respiratory mucosa in children with recurrent bronchitis. *European Respiratory Journal* 1992;**Suppl 5**:301.

Gaudier 1968 *{unpublished data only}*

Gaudier B, Lelong M. Carbocysteine to treat asthma in children [L'utilisation de la S-Carboxy Methyl Cystéine (LJ 206) dans l'asthme de l'enfant]. Laboratoires Joullie, Paris 1968.

Ginocchi 1978 *{published data only}*

Ginocchi G. Clinical effects of a mucolytic agent (Pol 65) in a pediatric statistical study [Effeti clinici di un mucoliyico (Pol 65) in una casistica pediatrica]. *Settimana Medica* 1978;**66**:391-408.

Gusberti 1985 *{published data only}*

Gusberti C, Bellazzi A, Lonati C, Modesti R. Clinical evaluation of a new synthetic derivative of acetylcysteine for treating respiratory inflammations in pediatric patients [Valutazione clinica di uno nuovo derivato sintetico dell'acido acetilsalicilico nella terapia di flogosi respiratorie di pazienti pediatrici]. *Archivio di Medicina Interna* 1985;**37**:123-9.

Henocq 1985 *{published data only}*

Henocq A, Moreau C, Mallet E, Sauger F, Menibus CH de. Changes in IgA levels in nasal mucus after upper respiratory tract diseases in infants treated with carbocysteine [Modifications du taux IgA du mucus nasal au décours des affections des voies aériennes supérieures du nourrisson traitées par la carbocistéine]. *Annales d'Oto-Laryngologie et de Chirurgie Cervico Faciale* 1985;**102**:373-5.

Hofmann 1980 *{published data only}*

Hofmann A. Oral acetylcystein in the treatment of bronchial asthma and chronic respiratory tract diseases [Orale anwendung von acetylcystein bei der behandlung von asthma bronchiale und chronischen erkrankungen der luftwege]. *Therapiewoche* 1980;**30**:2040-6.

Jean 1982 *{unpublished data only}*

Jean R, Gardair F. Efficacy on expectoration of acetylcysteine nebulization in pediatric patients [Utilisation du Fluimucil antibiotic 750 en aérosols chez le nourisson et l'enfant son efficacité d'expectoration]. Laboratoires Zambon, Paris 1982.

Leupold 1970 *{published data only}*

Leupold W von. Lung function in bronchial asthma during treatment with Mucosolvin [Die lungenfunktion bei asthma bronchiale unter der behandlung mit Mucosolvia]. *Das Deutsche Gesundheitswesen* 1970;**25**:1400-2.

Loscialpo Ramundo 1968 *{published data only}*

Loscialpo Ramundo D. On the use of the association of acetylcysteine and thiamphenicol glycinate in some pediatric pulmonary diseases [Sull'impiego associazone acetilcisteina-tiamfenicolo glicinato in alcune forme di patologia polmonare pediatrica]. *Clinical Pediatrics* 1968;**50**:43-56.

Mayaud 1980 *{published data only}*

Mayaud C, Lentschner C, Bouchoucha S, Marsac J. Thiamphenicol glycinate acetylcysteinate in the treatment of acute respiratory infections with mucostasis [L'acetylcysteinate de thiamphenicol glycinate dans le traitement des infections respiratoires aigues avec mucostase]. *European Journal of Respiratory Diseases Supplement* 1980;**61**(111):70-3.

Michael 1986 *{published data only}*

Michael P, Haase W. Treatment of acute and chronic bronchitis. Therapeutic experience with Pulmoclase [Behandlung akuter und chronischer bronchitis. Therapeutische erfahrungen mit Pulmoclase]. *Therapiewoche* 1986;**36**:4440-5.

Nigam 1981 *{published data only}*

Nigam BK. S-Carboxymethylcysteine (S-CMC) in bronchography technique. *Indian Journal of Chest Diseases and Allied Sciences* 1981;**23**:81-4.

Nikolic 1980 *{published data only}*

Nikolic P, Korac D. The influence of acetylcysteine on respiratory functions in children with recurrent bronchitis. *European Journal of Respiratory Diseases Supplement* 1980;**61**(111):141.

Olivieri 1979 *{published data only}*

Olivieri D, Pezza A, Polistina D, D'Agostino F. Clinical evaluation of a new pharmacological association in the therapy of acute and chronic bronchitis [Valutazione clinica di una nuova associazione farmacologica nella terapia delle broncopneumopatie acute e croniche]. *Archivio Monaldi per la Tisiologia e le Malattie dell'Apparato Respiratorio* 1979;**34**:29-41.

Plietz 1976 *{published data only}*

Plietz J. The treatment of bronchitic syndrome using Transbronchin in the practice. *Zeitschrift für Allgemeinmedizin (Stuttgart)* 1976;**52**:1832-4.

Poder 1982 *{unpublished data only}*

Poder G, Puskas J, Kelemen J, Gegesi Kiss A, Cserhati E. The effect of long term treatment with N-Acetylcysteine in infants with chronic obstructive bronchitis [Die Wirkung der Langzeitbehandlung mit N-Acetylcystein bei chronisch-obstruktiver Bronchitis im Sauglings- und Kleinkindalter]. Laboratoires Zambon (Pharmaceutical company), Paris 1982.

Ramenghi 1984 *{published data only}*

Ramenghi M, Sabayini G, Mengoni M. Combined antibiotic plus mucolytic treatment for recurrent bronchial diseases in infancy. *Current Therapeutic Research* 1984;**36**:664-7.

Ribeiro 1980 *{published data only}*

Ribeiro TM, Cunha LG, Santos M, Frenkiel S. Treatment of bronchial diseases in pediatrics. Results of the use of oral acetylcysteine in 80 cases. *European Journal of Respiratory Diseases Supplement* 1980;**61**(111):136-8.

Rudnik 1980 *{published data only}*

Rudnik J, Gawel J, Haluszka J, Kurzawa R, Mielnicka B, Majewska-Zalewska H, et al. Oral acetylcysteine treatment in children with chronic lung diseases. *European Journal of Respiratory Diseases Supplement* 1980;**61**(111):140.

Samsygina 1995 *{published data only}*

Samsygina G, Kazyukova T, Vykhristyuk O, Motina A, Tsaregorodtseva L, Dudina T. Acetylcysteine 100 in treatment of children with acute and chronic respiratory diseases: experience of use. *Pediatriya (Moscow)* 1995;**1**:76.

Santangelo 1985 *{published data only}*

Santangelo G, Lombardo S, Giannotti G. A combination of cefuroxime and N-acetyl-cysteine for the treatment of lower respiratory tract infections in children. *International Journal of Clinical Pharmacology, Therapy, and Toxicology* 1985;**23**:279-81.

Szekely 1980 *{published data only}*

Szekely E, Farkas E. Treatment of chronic bronchitis with oral acetylcysteine in children. *European Journal of Respiratory Diseases Supplement* 1980;**61**(111):142.

Trastotenojo 1984 *{published data only}*

Trastotenojo MS, Harsoyo N, Sachro AD, Soemantri AG, Said HW. Use of acetyl cysteine in respiratory tract disease in children. *Paediatrica Indonesiana* 1984;**24**:1-10.

Varricchio 2008 *{published data only}*

* Varricchio A, Capasso M, Di Giocchino M, Ciprandi G. Inhaled thiamphenicol and acetylcysteine in children with acute bacterial rhinopharyngitis. *International Journal of Immunopathology & Pharmacology* 2008;**21**:625-9.

Volkl 1992 *{published data only}*

Volkl VKP, Schneider B. Treatment of airway diseases with N-acetylcystein. An open therapeutic observational study involving 2512 patients. *Fortschritte der Medizin* 1992;**110**:346-50.

Zens 1967 *{published data only}*

Zens VM. Clinical trial with a mucolytic agent, acetylcysteine, in children with bronchitis [Klinische Erfahrungen mit Acetylcystein, einer mukoltytiscen Substanz, bei der Bronchitis im Kindesalter]. *Fortschritte der Medizin* 1967;**85**:206-7.

Zuppi 1984 *{published data only}*

Zuppi LJ, Croce J. Effect of oral route acetylcysteine on the spirometric parameters in children with asthma or rhinitis [Efeito da acetilcisteina oral sobre os parametros espirometricos em criancas asmaticas ou com rinite]. *Folha Médica* 1984;**89**:305-8.

Additional references

Anonymous 2000a

Anonymous. Acetylcysteine. In: McVoy GK editor(s). American Hospital Formulary System Drug Information. Bethesda, USA: American Society of Health-System Pharmacists Incorporation, 2000:472-4.

Anonymous 2000b

Anonymous. Acetylcysteine. Anonymous. Drug Facts and Comparisons 2000. 4th Edition. Saint Louis, USA: Facts and Comparisons, 2000:677-9.

Boluyt 2008

Boluyt N, Tjosvold L, Lefebvre C, Klassen TP, Offringa M. Usefulness of systematic review search strategies in finding child health systematic reviews in MEDLINE. *Archives of Pediatrics and Adolescent Medicine* 2008;**162**(2):111-6.

Bricks 1996

Bricks LF, Leone C. Use of medicines by children attending nursery schools. *Revista de Saúde Pública* 1996;**30**:527-35.

Bücheler 2002

Bücheler R, Schwab M, Mörike K, Kalchthaler B, Mohr H, Schröder H, et al. Off label prescribing to children in primary care in Germany: retrospective cohort study. *BMJ* 2002;**324**(7349):1311-2.

Cano Garcinuño 2013

Cano Garcinuño A, Casares Alonso I, Rodríguez Barbero J, Pérez García I, Blanco Quirós A. Prescription of systemic cold and cough drugs to children 0-13 years old. An unresolved problem. *Anales de Pediatría* 2013;**78**(1):43-50.

Cates 2003 [Computer program]

Cates C. Visual Rx. Online NNT Calculator (http://www.nntonline.net/). nntonline, 2003.

Cazzato 2001

Cazzato T, Pandolfi C, Campi R, Bonati M. Drug prescribing in out-patient children in Southern Italy. *European Journal of Clinical Pharmacology* 2001;**57**:611-6.

Chalumeau 2000

Chalumeau M, Treluyer JM, Salanave B, Assathiany R, Cheron G, Crocheton N, et al. Off label and unlicensed drug use among French office based paediatricians. *Archives of Disease in Childhood* 2000;**83**(6):502-5.

Chang 2006

Chang AB, Glomb WB. Guidelines for evaluating chronic cough in pediatrics. *Chest* 2006;**129**(Suppl):260-83.

Collet 1991

Collet JP, Bossard N, Floret D, Gillet J, Honegger D, Boissel JP. Drug prescription in young children: results of a survey in France. *European Journal of Clinical Pharmacology* 1991;**41**:489-91.

Cumberland Pharmaceuticals 2008

Cumberland Pharmaceuticals. Acetadote(r) iv injection, acetylcysteine iv injection. Product information 2008.

Delgado-Rodriguez 2004

Delgado-Rodriguez M, Llorca J. Bias. *Journal of Epidemiology and Community Health* 2004;**58**:635-41.

Duijvestijn 1997

Duijvestijn YC, Gerritsen J, Brand PL. Acetylcysteine in children with lung disorders prescribed by one-third of family physicians: no support in the literature. *Nederlands Tijdschrift Voor Geneeskunde* 1997;**141**:826-30.

Duijvestijn 1999

Duijvestijn YC, Brand PL. Systematic review of N-acetylcysteine in cystic fibrosis. *Acta Paediatrica* 1999;**88**:38-41.

EMEA 2001

European Agency for the Evaluation of Medicinal Products. International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use. Clinical investigation of medicinal products in the paediatric population (ICH Topic E11). http://www.emea.europa.eu/pdfs/human/ich/271199en.pdf 2001 (accessed 15 October 2007).

Halna 2005

Halna M, Leblond P, Aissi E, Dumonceaux A, Delepoulle F, El Kohen R, et al. Impact of the consensus conference on outpatient treatment of infant bronchiolitis. *Presse Médicale* 2005;**34**:277-81.

Harris 1967

Harris RL, Riley HD. Reactions to aerosol medication in infants and children. *JAMA* 1967;**201**:953-5.

Higgins 2003

Higgins JPT, Thompson SG, Deeks JD, Altman G. Measuring inconsistency in meta-analysis. *BMJ* 2003;**327**:557-60.

Horen 2002

Horen B, Montastruc J-L, Lapeyre-Mestre M. Adverse drug reactions and off-label drug use in paediatric outpatients. *Journal of Clinical Pharmacology* 2002;**54**:665-70.

Horwitz 1980

Horwitz RI, Feinstein AR. The problem of "protopathic bias" in case-control studies. *American Journal of Medicine* 1980;**68**:255-8.

Hughes 1994

Hughes J, Gill A, Leach HJ, Nunn AJ, Billingham I, Ratcliffe J, et al. A prospective study of the adverse effects of midazolam on withdrawal in critically ill children. *Acta Paediatrica* 1994;**83**:1194-9.

Mallet 2011

Mallet P, Mourdi N, Dubus J-C, Bavoux F, Boyer-Gervoise M-J, Jean-Pastor M-J, et al. Respiratory paradoxical adverse drug reactions associated with acetylcysteine and carbocysteine systemic use in paediatric patients: a national survey. *PLoS One* 2011;**6**:e22792.

Medici 1979

Medici TC, Radielovic P. Effects of drugs on mucus glycoproteins and water in bronchial secretion. *Journal of International Medical Research* 1979;**7**(5):434-42.

Mourdi 2010

Mourdi N, Dubus JC, Bavoux F, Boyer-Gervoise M, Jean-Pastor MJ, Chalumeau M. Mucolytic drugs: towards a contraindication in infants. *Archives de Pédiatrie* 2010;**17**:735-6.

Naranjo 1981

Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. *Clinical Pharmacology and Therapeutics* 1981;**30**:239-45. [MEDLINE: 7249508]

Poole 2012

Poole P, Black PN, Cates CJ. Mucolytic agents for chronic bronchitis or chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews* 2012, Issue 8. [DOI: 10.1002/14651858.CD001287.pub4]

RevMan 2012 [Computer program]

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.2. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012.

Salas 1999

Salas M, Hofman A, Strieker BHC. Confounding by indication: an example of variation in the use of epidemiologic terminology. *American Journal of Epidemiology* 1999;**149**:981-3.

Sanz 1988

Sanz EJ, Boada JN. Drug utilization by children in Tenerife Island. *European Journal of Clinical Pharmacology* 1988;**34**:495-9.

Sen 2011

Sen EF, Verhamme KM, Felisi M, 't Jong GW, Giaquinto C, Picelli G, et al. Effects of safety warnings on prescription rates of cough and cold medicines in children below 2 years of age. *British Journal of Clinical Pharmacology* 2011;**71**:943-50.

Shields 2008

Shields MD, Bush A, Everard ML, McKenzie S, Primhak R, British Thoracic Society Cough Guideline Group. BTS guidelines: recommendations for the assessment and management of cough in children. *Thorax* 2008;**63**(Suppl 3):iii1-15.

Smith 2012

Smith SM, Schroeder K, Fahey T. Over-the-counter (OTC) medications for acute cough in children and adults in ambulatory settings. *Cochrane Database of Systematic Reviews* 2012, Issue 8. [DOI: 10.1002/14651858.CD001831.pub4]

WHO 2007

WHO Child Growth Standards. Weight-for-age. http://www.who.int/childgrowth/standards/weight_for_age/en/ 2013 (accessed 1 April 2013).

Wohl 1998

Wohl MEB. Developmental physiology of the respiratory system. In: Chernick V, Boat TF editor(s). Kendig's Disorders of the Respiratory Tract in Children. Vol. **6th**, Philadelphia, USA: WB Saunders Company, 1998.

References to other published versions of this review

Duijvestijn 2009

Duijvestijn YCM, Mourdi N, Smucny J, Pons G, Chalumeau M. Acetylcysteine and carbocysteine for acute upper and lower respiratory tract infections in paediatric patients without chronic broncho-pulmonary disease. *Cochrane Database of Systematic Reviews* 2009, Issue 1. [DOI: 10.1002/14651858.CD003124.pub3]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Bellomo 1972

Methods	RCT All participants received thiamphenicol with or without acetylcysteine
Participants	59 paediatric outpatients (22 < 1 year; 28 1 to 5 years; 9 > 5 years) seen for acute bronchitis or broncho-pulmonary infections
Interventions	Oral acetylcysteine 13.8 mg/kg/day 2 to 4 times a day for 6 to 7 days average (maximum 14 days)
Outcomes	Clinical: duration of febrile state, dyspnoea, thoracic semeiologic alterations, cough
Notes	Italian

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Only reported that allocation was done randomly
Allocation concealment (selection bias)	Unclear risk	Nothing in the text deals with allocation concealment

Bellomo 1972 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Only reported that treatment was randomly assigned
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Nothing in the text deals with blinding of outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Nothing in the results clearly mentioned the number of patients used in the analysis
Selective reporting (reporting bias)	Low risk	All the judgement criteria were reported in the analysis

Biscatti 1972

Methods	RCT All participants received some kind of antibiotic
Participants	50 children (29 < 2 years; 21 > 2 years) hospitalised for acute respiratory infections
Interventions	Oral acetylcysteine 100 mg/day under 2 years 200 mg/day between 2 and 4 years 300 mg/day above 4 years for 6 days
Outcomes	Clinical: cough, dyspnoea, thoracic semeiologic alteration, temperature reading Biological: ESR and leucocyte count
Notes	Italian Possibly not a comparable treatment because various antibiotics were used

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	It is only mentioned that treatments were assigned randomly
Allocation concealment (selection bias)	Unclear risk	Nothing is mentioned about allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Nothing is mentioned about blinding of participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Nothing is mentioned about blinding of outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients are mentioned in the analyses and the tables

Biscatti 1972 *(Continued)*

Selective reporting (reporting bias)	Low risk	All criteria mentioned in 'Methods' were mentioned in the analysis

Fiocchi 1989

Methods	RCT All participants received antibiotics if necessary
Participants	100 paediatric ambulatory participants (all > 2 years) seen in a paediatric department for acute lower respiratory infections
Interventions	Oral acetylcysteine 20 mg/kg/day 3 times daily for 28 days
Outcomes	Clinical: cough, cough productivity and thoracic semeilogic alteration PFT
Notes	Italian Side effects: 2 participants vomited in the acetylcysteine group, with 1 drop-out

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	It is only mentioned that randomisation was based on a list
Allocation concealment (selection bias)	Unclear risk	Nothing is mentioned about allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Nothing is mentioned about blinding of participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Nothing is mentioned about blinding of outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients are mentioned in the analyses and the tables
Selective reporting (reporting bias)	Low risk	All the criteria mentioned in 'Methods' were mentioned in the analysis

Malka 1990

Methods	RCT All participants received antibiotics if necessary
Participants	106 paediatric ambulatory participants (2 to 12 years) seen in general practice for acute bronchitis
Interventions	Oral carbocysteine for 7 days: 200 mg/day under 5 years. 300 mg/day above 5 years

Malka 1990 *(Continued)*

Outcomes	Clinical: cough, expectoration, bronchial congestion, dyspnoea PFT
Notes	French 9 participants with side effects (in the carbocysteine group: 2 nausea, 3 diarrhoea, 1 stomach pain; in the placebo group: 1 nausea, 2 stomach pain)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomised multicentre trial"
Allocation concealment (selection bias)	High risk	Quote: "The lack of respect in the order of the randomisation list..."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Double blinding"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Nothing in the text deals with blinding of outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "The patients included for wrong reasons or who did not respect the protocol were included in the analysis"
Selective reporting (reporting bias)	Low risk	All the judgement criteria were reported in the analysis

Nakayama 1977

Methods	RCT Participants received bronchodilators, antibiotics, antihistamine if previously treated
Participants	152 paediatric outpatients (0 to 18 years) bronchial asthma or acute bronchitis
Interventions	Oral carbocysteine 30 mg/kg/day (administered in 3 or 4 doses) for 7 days
Outcomes	Clinical: overall assessment, cough, stridor, expectoration PFT
Notes	French Results tables were not available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "a table of random administration of products"

Nakayama 1977 *(Continued)*

Allocation concealment (selection bias)	Low risk	Quote: "to ensure the impossibility of identifying the products, the random distribution, the secrecy of the key table..."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "aspect, characteristics, taste, flavour and packaging were verified by a independent person"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The data statistics analyses were performed by a independent person"
Incomplete outcome data (attrition bias) All outcomes	High risk	In the 'Results' section, it is mentioned that not all the patients were included in the statistical analyses
Selective reporting (reporting bias)	Low risk	All the criteria mentioned in the 'Methods' section were mentioned in the 'Results' section

Zanini 1974

Methods	RCT In treatment group: 15 children received antibiotics; 4 received inhaled acetylcysteine In control group: 8 children received antibiotics
Participants	30 children (18 < 1 year; 12 > 1 year) hospitalised for acute respiratory infections
Interventions	Oral carbocysteine from 100 to 400 mg/day depending on age for 5 to 9 days
Outcomes	Clinical: cough, dyspnoea, temperature level, appetite, general condition
Notes	Italian

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "The patients were assigned randomly"
Allocation concealment (selection bias)	Unclear risk	The text did not mention anything about allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "we had noticed the better efficacy of one of the produce in looking clinically at the therapeutic results"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "we had noticed the better efficacy of one of the produce in looking clinically at the therapeutic results"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All the patients included were mentioned in the analysis

Zanini 1974 *(Continued)*

Selective reporting (reporting bias)	Low risk	All the relevant criteria were mentioned in the analysis

AC: acetylcysteine
ESR: erythrocyte sedimentation rate
Gastralgia: localised stomach ache
PFT: pulmonary function tests
RCT: randomised controlled trial

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

Study	Reason for exclusion
Amir 1985	No control group; chronic disease
Anonymous 1987	No control group
Baldini 1989	Active control treatment
Banovcin 1990	Non-randomised; active control treatment
Banovcin 1992	Non-randomised; active control treatment
Bellomo 1967a	Non-randomised
Bellomo 1967b	No control group
Bellomo 1973	Active control treatment
Berger 1978	No control group; chronic disease
Berni 1983	Active control treatment
Boner 1984	No control group
Camurri 1990	Active control treatment
Caramia 1984	No control group
Careddu 1989	Active control treatment
Castello 1979	No control group
Chalumeau 2002	No control group
Dano 1971	No control group
Egreteau 1992	Chronic disease
Gaudier 1968	No control group
Ginocchi 1978	No control group
Gusberti 1985	Active control treatment

Study	Reason for exclusion
Henocq 1985	No placebo Type of outcome measures
Hofmann 1980	No placebo Chronic disease
Jean 1982	No placebo
Leupold 1970	No placebo
Loscialpo Ramundo 1968	No control group
Mayaud 1980	No placebo
Michael 1986	No placebo
Nigam 1981	No placebo Chronic disease
Nikolic 1980	No placebo
Olivieri 1979	Chronic diseases No control group
Plietz 1976	Chronic diseases No control group
Poder 1982	Chronic diseases No control group
Ramenghi 1984	No control group
Ribeiro 1980	Chronic diseases No control group
Rudnik 1980	Chronic diseases No control group
Samsygina 1995	Chronic disease No randomisation Active control treatment
Santangelo 1985	No control group
Szekely 1980	Chronic diseases No control group
Trastotenojo 1984	No randomisation
Varricchio 2008	Antibiotic treatment only in treatment group Type of disease
Volkl 1992	No control group
Zens 1967	Chronic diseases No control group

Study	Reason for exclusion
Zuppi 1984	Chronic diseases

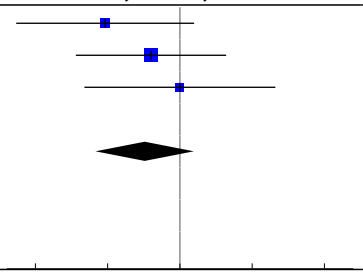
DATA AND ANALYSES

Comparison 1. Febrile state (AC or CC versus placebo)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Febrile state after 6 days	3	139	Risk Difference (M-H, Random, 95% CI)	-0.05 [-0.12, 0.02]
2 Febrile state after 6 days	3	139	Risk Ratio (M-H, Random, 95% CI)	0.21 [0.02, 1.77]

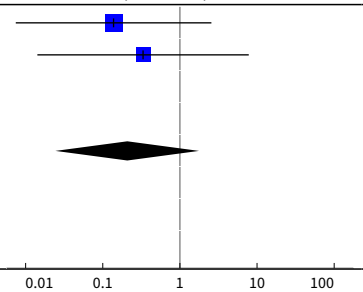
Analysis 1.1. Comparison 1 Febrile state (AC or CC versus placebo), Outcome 1 Febrile state after 6 days.

Study or subgroup	Treatment (AC or CC) n/N	Placebo n/N	Risk Difference M-H, Random, 95% CI	Weight	Risk Difference M-H, Random, 95% CI
Bellomo 1972	0/30	3/29		30.58%	-0.1[-0.23,0.02]
Biscatti 1972	0/25	1/25		42.86%	-0.04[-0.14,0.06]
Zanini 1974	0/19	0/11		26.55%	0[-0.13,0.13]
Total (95% CI)	**74**	**65**		**100%**	**-0.05[-0.12,0.02]**
Total events: 0 (Treatment (AC or CC)), 4 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.4, df=2(P=0.5); I^2=0%					
Test for overall effect: Z=1.4(P=0.16)					



Analysis 1.2. Comparison 1 Febrile state (AC or CC versus placebo), Outcome 2 Febrile state after 6 days.

Study or subgroup	Treatment (AC or CC) n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Bellomo 1972	0/30	3/29		53.84%	0.14[0.01,2.56]
Biscatti 1972	0/25	1/25		46.16%	0.33[0.01,7.81]
Zanini 1974	0/19	0/11			Not estimable
Total (95% CI)	**74**	**65**		**100%**	**0.21[0.02,1.77]**
Total events: 0 (Treatment (AC or CC)), 4 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.16, df=1(P=0.69); I^2=0%					
Test for overall effect: Z=1.44(P=0.15)					

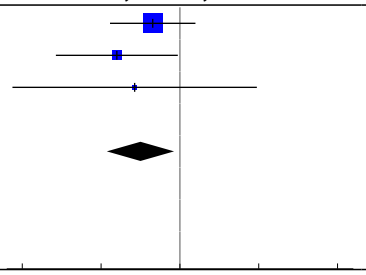


Comparison 2. Cough (AC or CC versus placebo)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cough after 6 to 7 days	3	139	Risk Difference (M-H, Random, 95% CI)	-0.10 [-0.19, -0.01]
2 Cough after 6 to 7 days	3	139	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.12, 1.20]
3 Cough at the end of treatment (= 28 days)	1	100	Risk Difference (M-H, Fixed, 95% CI)	-0.03 [-0.13, 0.07]
3.1 Subgroup = bronchitis	1	48	Risk Difference (M-H, Fixed, 95% CI)	-0.07 [-0.25, 0.11]
3.2 Subgroup = tracheitis	1	52	Risk Difference (M-H, Fixed, 95% CI)	0.01 [-0.10, 0.12]
4 Cough at the end of treatment (= 28 days)	1	100	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.16, 2.76]
4.1 Subgroup = bronchitis	1	48	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.10, 2.83]
4.2 Subgroup = tracheitis	1	52	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [0.08, 19.09]

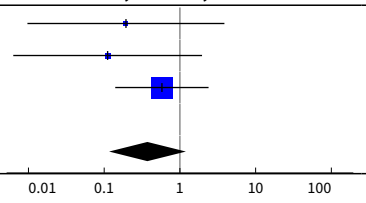
Analysis 2.1. Comparison 2 Cough (AC or CC versus placebo), Outcome 1 Cough after 6 to 7 days.

Study or subgroup	AC or CC n/N	Placebo n/N	Risk Difference M-H, Random, 95% CI	Weight	Risk Difference M-H, Random, 95% CI
Bellomo 1972	0/30	2/29		61.99%	-0.07[-0.18,0.04]
Biscatti 1972	0/25	4/25		30.43%	-0.16[-0.31,-0.01]
Zanini 1974	3/19	3/11		7.57%	-0.11[-0.42,0.2]
Total (95% CI)	**74**	**65**		**100%**	**-0.1[-0.19,-0.01]**
Total events: 3 (AC or CC), 9 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.97, df=2(P=0.62); I^2=0%					
Test for overall effect: Z=2.3(P=0.02)					

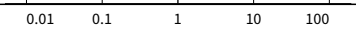


Analysis 2.2. Comparison 2 Cough (AC or CC versus placebo), Outcome 2 Cough after 6 to 7 days.

Study or subgroup	AC or CC n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Bellomo 1972	0/30	2/29		15.27%	0.19[0.01,3.87]
Biscatti 1972	0/25	4/25		16.61%	0.11[0.01,1.96]
Zanini 1974	3/19	3/11		68.12%	0.58[0.14,2.39]
Total (95% CI)	**74**	**65**		**100%**	**0.37[0.12,1.2]**



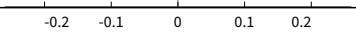
Study or subgroup	AC or CC n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Total events: 3 (AC or CC), 9 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.39, df=2(P=0.5); I^2=0%					
Test for overall effect: Z=1.66(P=0.1)					



Favours experimental (AC or CC) — Favours control (placebo)

Analysis 2.3. Comparison 2 Cough (AC or CC versus placebo), Outcome 3 Cough at the end of treatment (= 28 days).

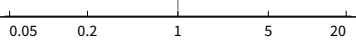
Study or subgroup	AC n/N	Placebo n/N	Risk Difference M-H, Fixed, 95% CI	Weight	Risk Difference M-H, Fixed, 95% CI
2.3.1 Subgroup = bronchitis					
Fiocchi 1989	2/27	3/21		47.94%	-0.07[-0.25,0.11]
Subtotal (95% CI)	**27**	**21**		**47.94%**	**-0.07[-0.25,0.11]**
Total events: 2 (AC), 3 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.75(P=0.45)					
2.3.2 Subgroup = tracheitis					
Fiocchi 1989	1/23	1/29		52.06%	0.01[-0.1,0.12]
Subtotal (95% CI)	**23**	**29**		**52.06%**	**0.01[-0.1,0.12]**
Total events: 1 (AC), 1 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.17(P=0.87)					
Total (95% CI)	**50**	**50**		**100%**	**-0.03[-0.13,0.07]**
Total events: 3 (AC), 4 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.67, df=1(P=0.41); I^2=0%					
Test for overall effect: Z=0.54(P=0.59)					
Test for subgroup differences: Chi^2=0.53, df=1 (P=0.46), I^2=0%					



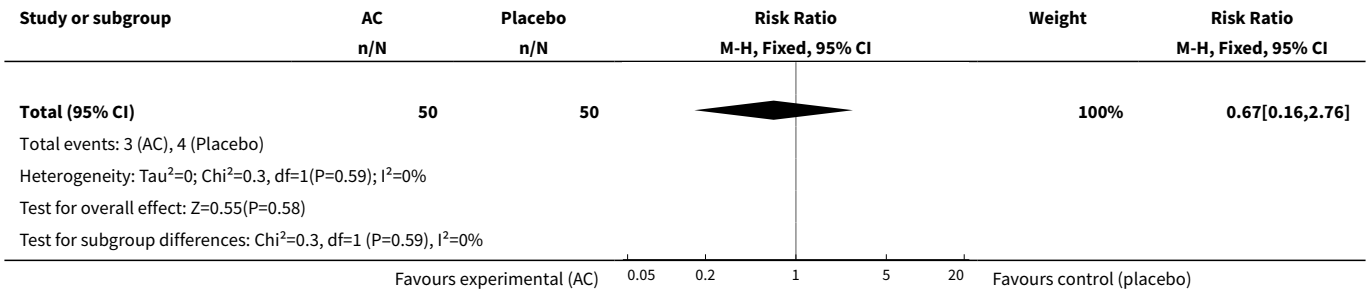
Favours experimental (AC) — Favours control (placebo)

Analysis 2.4. Comparison 2 Cough (AC or CC versus placebo), Outcome 4 Cough at the end of treatment (= 28 days).

Study or subgroup	AC n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.4.1 Subgroup = bronchitis					
Fiocchi 1989	2/27	3/21		79.23%	0.52[0.1,2.83]
Subtotal (95% CI)	**27**	**21**		**79.23%**	**0.52[0.1,2.83]**
Total events: 2 (AC), 3 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.76(P=0.45)					
2.4.2 Subgroup = tracheitis					
Fiocchi 1989	1/23	1/29		20.77%	1.26[0.08,19.09]
Subtotal (95% CI)	**23**	**29**		**20.77%**	**1.26[0.08,19.09]**
Total events: 1 (AC), 1 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.17(P=0.87)					



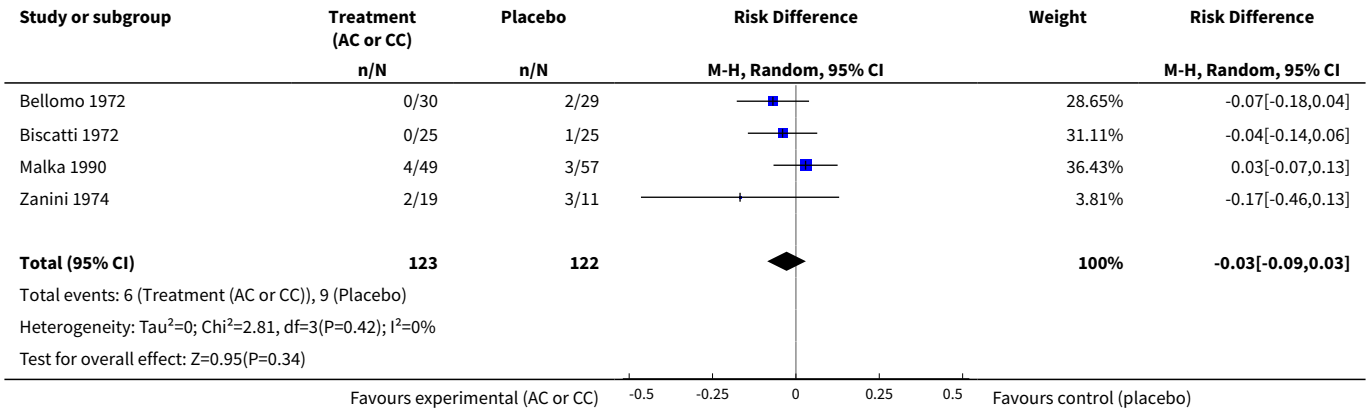
Favours experimental (AC) — Favours control (placebo)



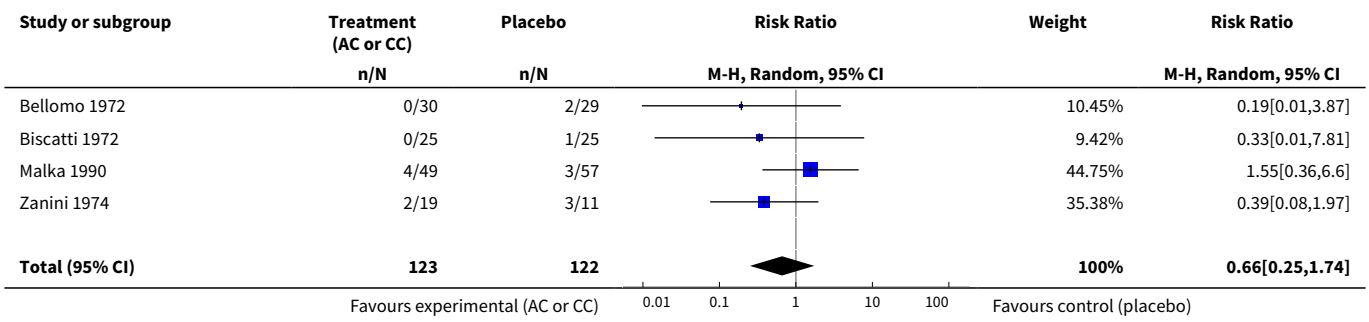
Comparison 3. Dyspnoea (AC or CC versus placebo)

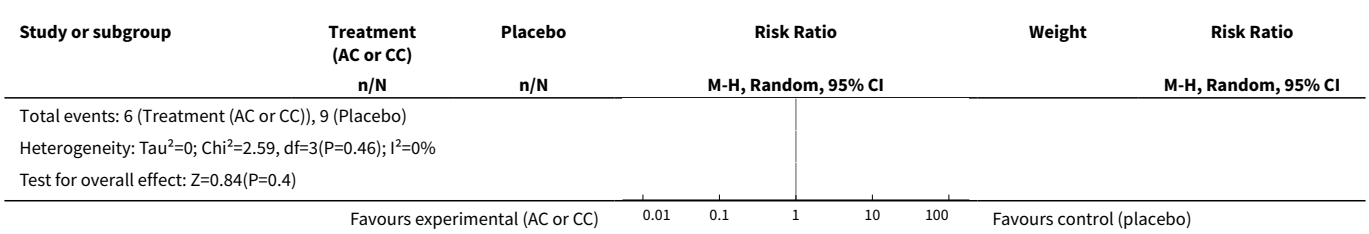
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Dyspnoea after 6 to 7 days	4	245	Risk Difference (M-H, Random, 95% CI)	-0.03 [-0.09, 0.03]
2 Dyspnoea after 6 to 7 days	4	245	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.25, 1.74]

Analysis 3.1. Comparison 3 Dyspnoea (AC or CC versus placebo), Outcome 1 Dyspnoea after 6 to 7 days.



Analysis 3.2. Comparison 3 Dyspnoea (AC or CC versus placebo), Outcome 2 Dyspnoea after 6 to 7 days.

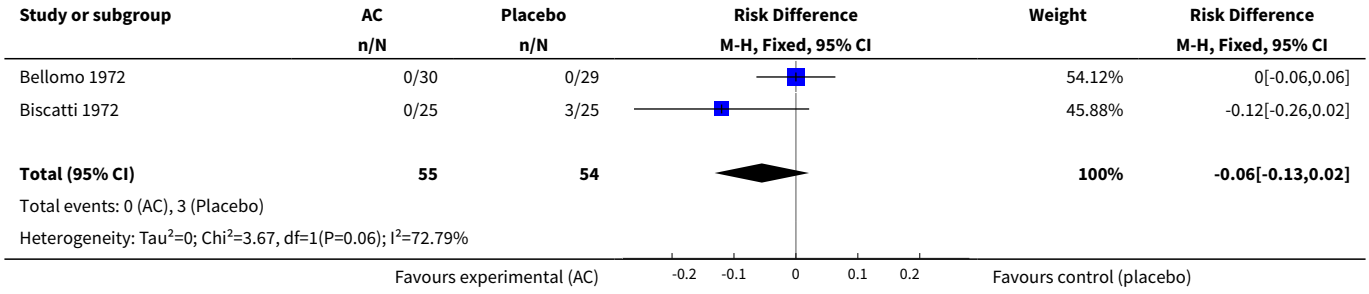


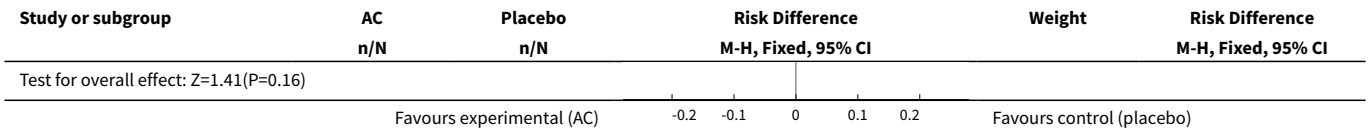


Comparison 4. Thoracic semeiologic alterations (AC versus placebo)

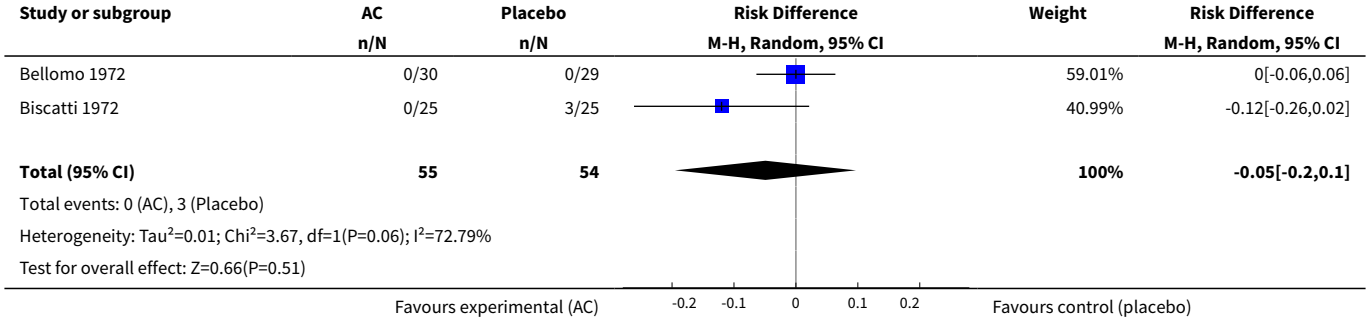
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Thoracic semeiologic alterations after 5 days	2	109	Risk Difference (M-H, Fixed, 95% CI)	-0.06 [-0.13, 0.02]
2 Thoracic semeiologic alterations after 5 days	2	109	Risk Difference (M-H, Random, 95% CI)	-0.05 [-0.20, 0.10]
3 Thoracic semeiologic alterations after 5 days	2	109	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.01, 2.63]
4 Thoracic semeiologic alterations at the end of treatment (= 28 days)	1	100	Risk Difference (M-H, Fixed, 95% CI)	-0.14 [-0.25, -0.03]
4.1 Subgroup = bronchitis	1	48	Risk Difference (M-H, Fixed, 95% CI)	-0.11 [-0.27, 0.06]
4.2 Subgroup = tracheitis	1	52	Risk Difference (M-H, Fixed, 95% CI)	-0.17 [-0.32, -0.02]
5 Thoracic semeiologic alterations at the end of treatment (= 28 days)	1	100	Risk Ratio (M-H, Fixed, 95% CI)	0.17 [0.03, 0.99]
5.1 Subgroup = bronchitis	1	48	Risk Ratio (M-H, Fixed, 95% CI)	0.26 [0.03, 2.32]
5.2 Subgroup = tracheitis	1	52	Risk Ratio (M-H, Fixed, 95% CI)	0.11 [0.01, 1.95]

Analysis 4.1. Comparison 4 Thoracic semeiologic alterations (AC versus placebo), Outcome 1 Thoracic semeiologic alterations after 5 days.

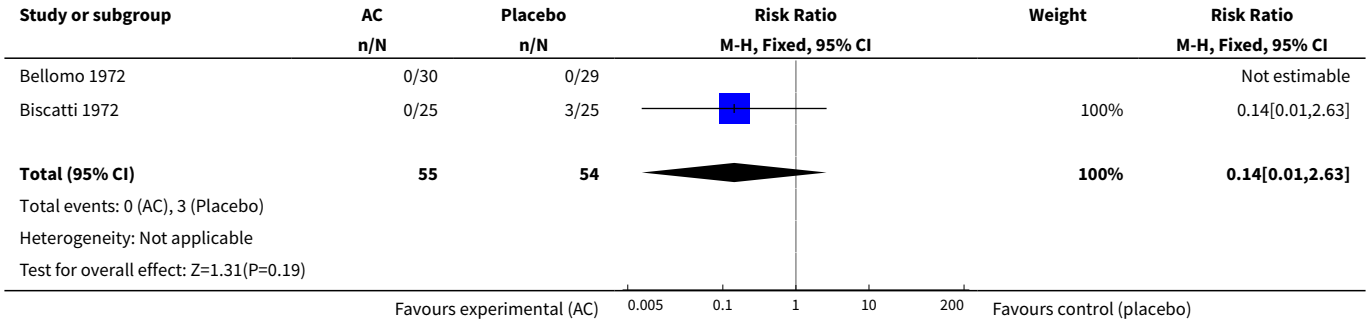




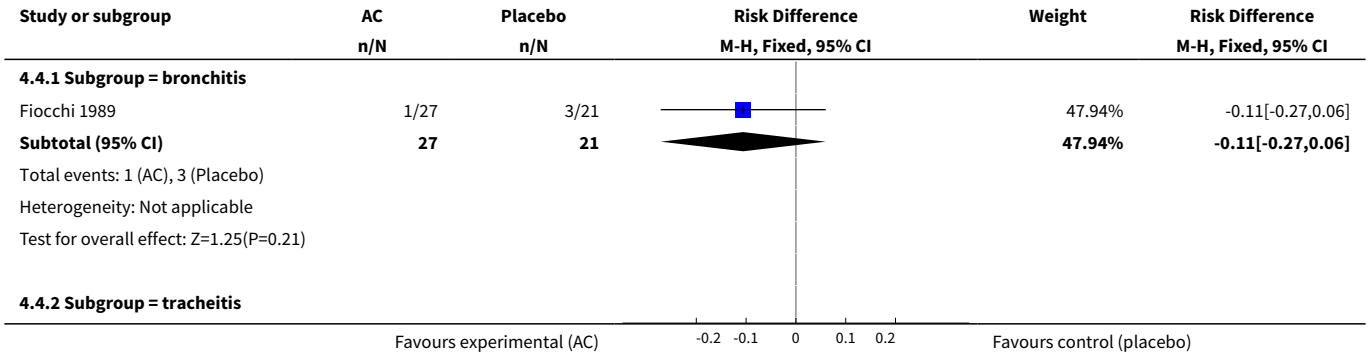
Analysis 4.2. Comparison 4 Thoracic semeiologic alterations (AC versus placebo), Outcome 2 Thoracic semeiologic alterations after 5 days.

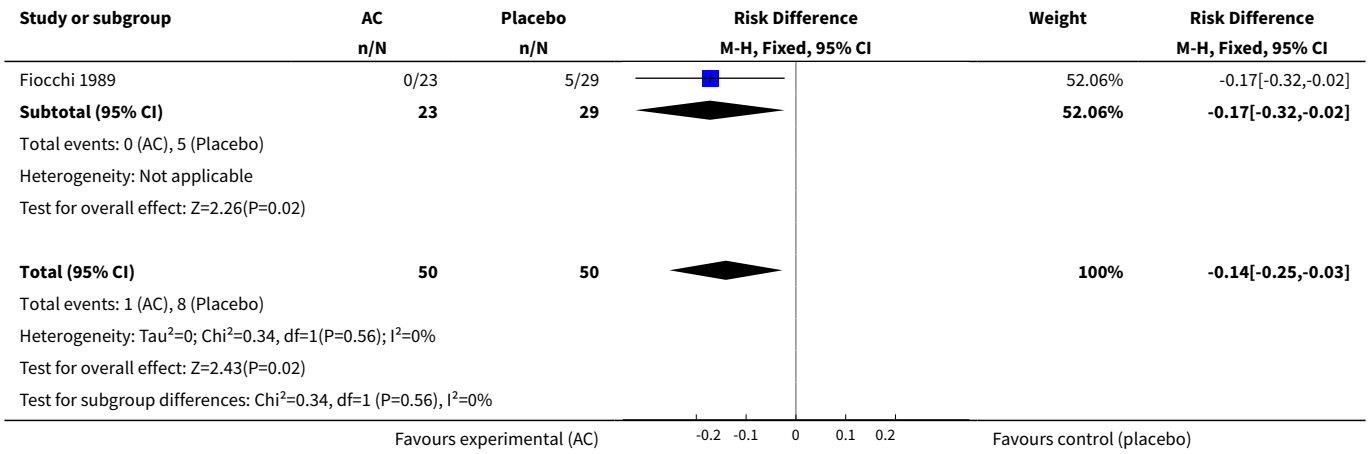


Analysis 4.3. Comparison 4 Thoracic semeiologic alterations (AC versus placebo), Outcome 3 Thoracic semeiologic alterations after 5 days.

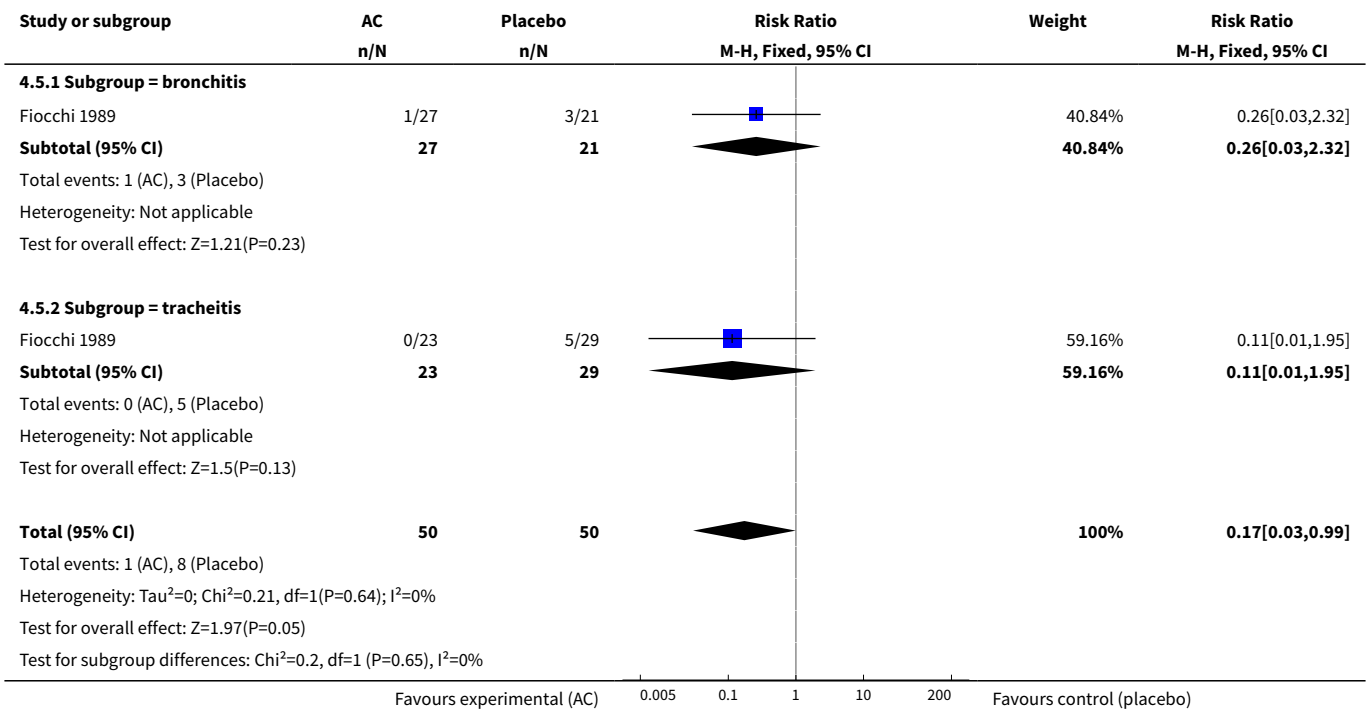


Analysis 4.4. Comparison 4 Thoracic semeiologic alterations (AC versus placebo), Outcome 4 Thoracic semeiologic alterations at the end of treatment (= 28 days).





Analysis 4.5. Comparison 4 Thoracic semeiologic alterations (AC versus placebo), Outcome 5 Thoracic semeiologic alterations at the end of treatment (= 28 days).

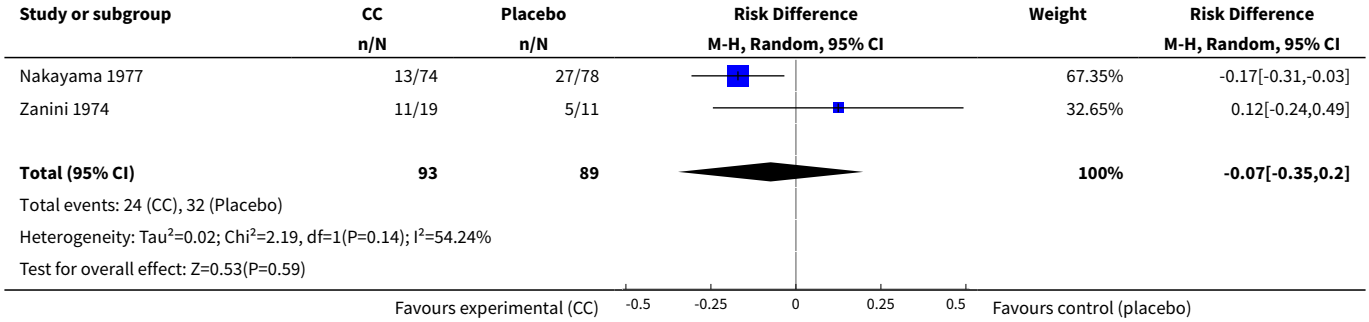


Comparison 5. General condition (CC versus placebo)

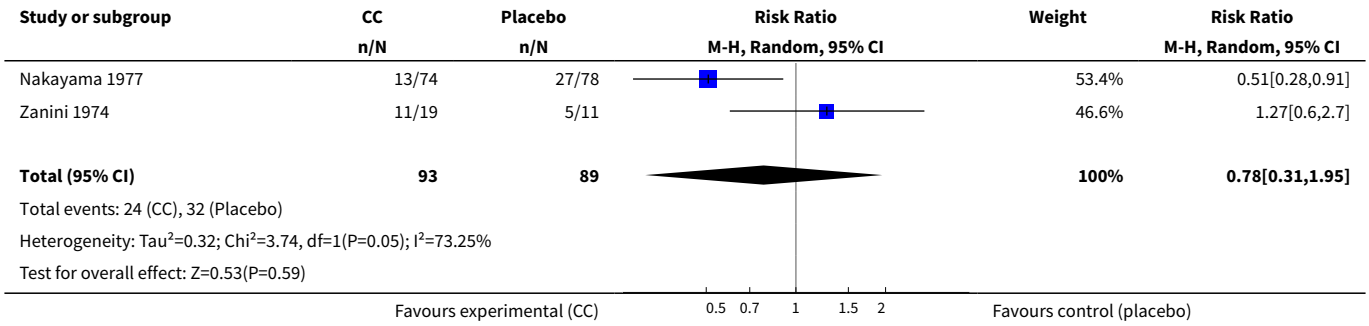
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Bad general condition after 6 to 7 days	2	182	Risk Difference (M-H, Random, 95% CI)	-0.07 [-0.35, 0.20]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Bad general condition after 6 to 7 days	2	182	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.31, 1.95]

Analysis 5.1. Comparison 5 General condition (CC versus placebo), Outcome 1 Bad general condition after 6 to 7 days.



Analysis 5.2. Comparison 5 General condition (CC versus placebo), Outcome 2 Bad general condition after 6 to 7 days.

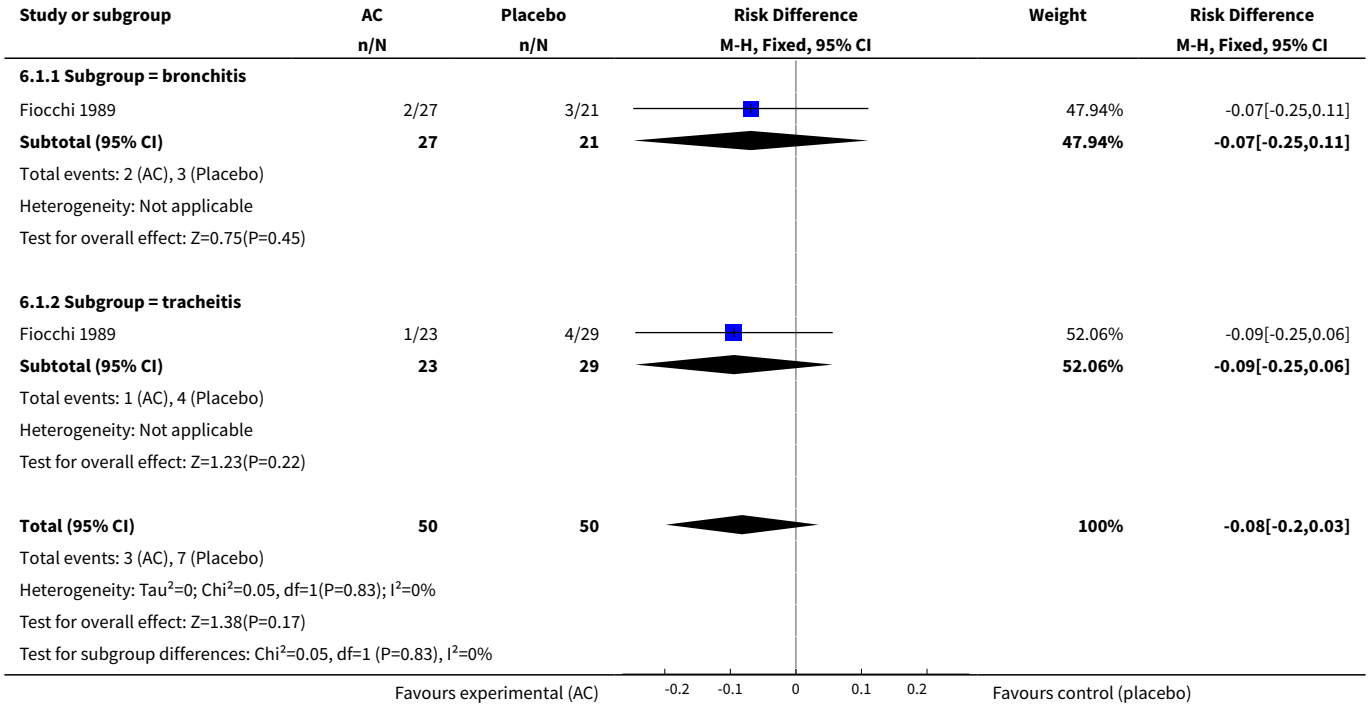


Comparison 6. Cough productivity (AC versus placebo)

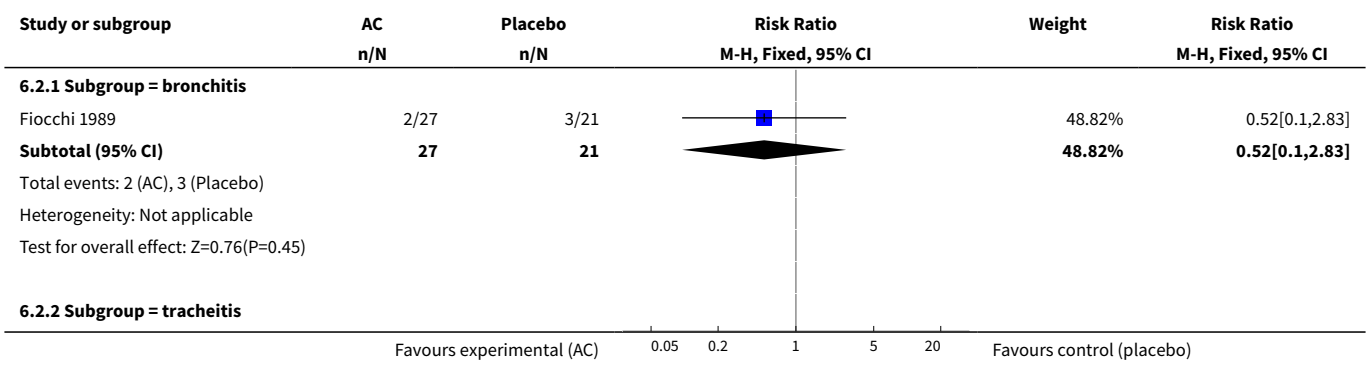
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cough productivity at the end of treatment (= 28 days)	1	100	Risk Difference (M-H, Fixed, 95% CI)	-0.08 [-0.20, 0.03]
1.1 Subgroup = bronchitis	1	48	Risk Difference (M-H, Fixed, 95% CI)	-0.07 [-0.25, 0.11]
1.2 Subgroup = tracheitis	1	52	Risk Difference (M-H, Fixed, 95% CI)	-0.09 [-0.25, 0.06]

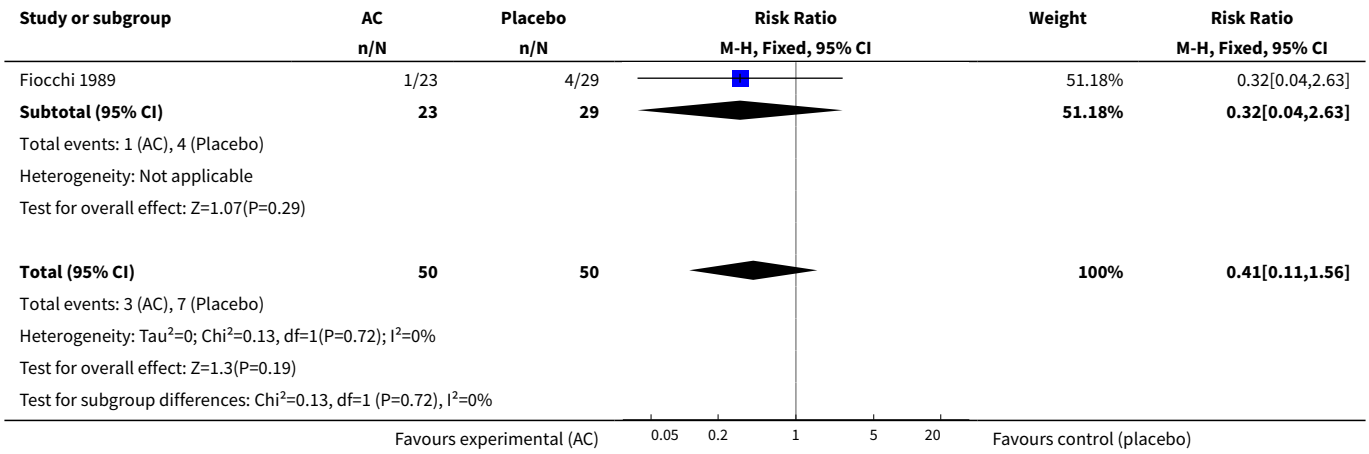
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Cough productivity at the end of treatment (= 28 days)	1	100	Risk Ratio (M-H, Fixed, 95% CI)	0.41 [0.11, 1.56]
2.1 Subgroup = bronchitis	1	48	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.10, 2.83]
2.2 Subgroup = tracheitis	1	52	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.04, 2.63]

Analysis 6.1. Comparison 6 Cough productivity (AC versus placebo), Outcome 1 Cough productivity at the end of treatment (= 28 days).



Analysis 6.2. Comparison 6 Cough productivity (AC versus placebo), Outcome 2 Cough productivity at the end of treatment (= 28 days).

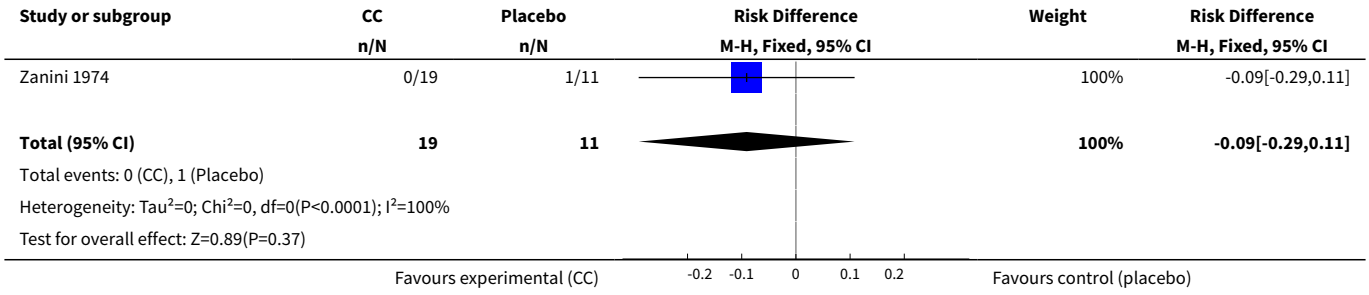




Comparison 7. Appetite (CC versus placebo)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Appetite trouble at the end of treatment (5 to 9 days)	1	30	Risk Difference (M-H, Fixed, 95% CI)	-0.09 [-0.29, 0.11]

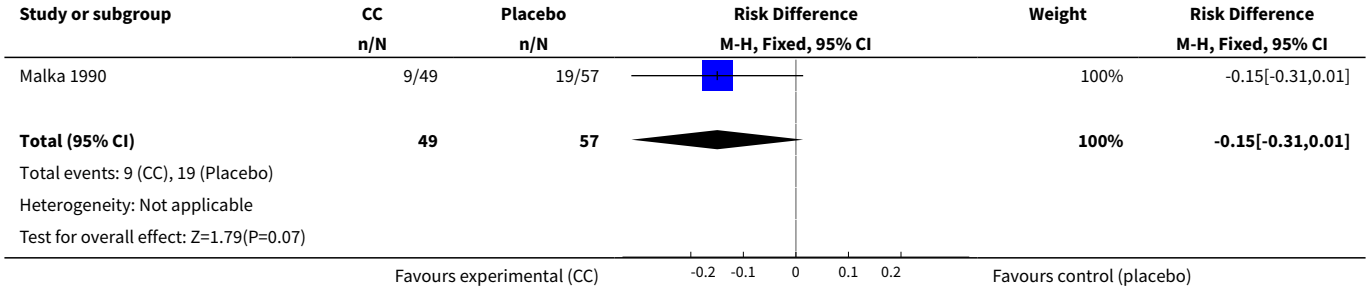
Analysis 7.1. Comparison 7 Appetite (CC versus placebo), Outcome 1 Appetite trouble at the end of treatment (5 to 9 days).



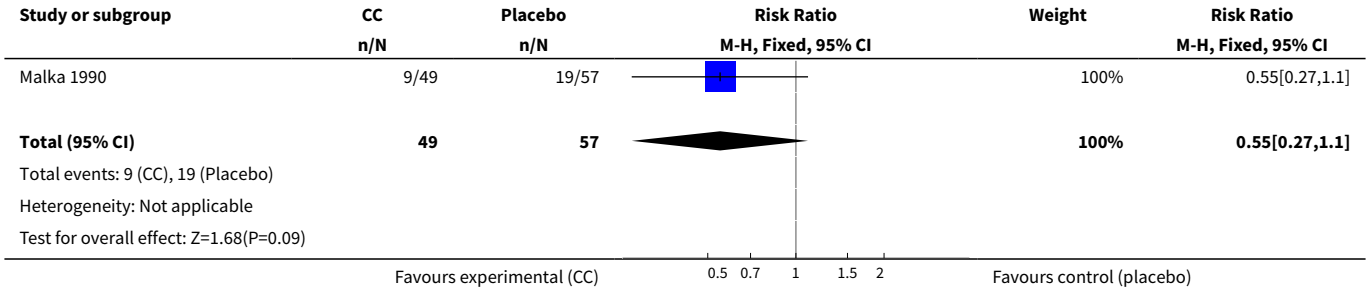
Comparison 8. Expectoration (CC versus placebo)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Expectoration at the end of treatment (= 7 days)	1	106	Risk Difference (M-H, Fixed, 95% CI)	-0.15 [-0.31, 0.01]
2 Expectoration at the end of treatment (= 7 days)	1	106	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.27, 1.10]

Analysis 8.1. Comparison 8 Expectoration (CC versus placebo), Outcome 1 Expectoration at the end of treatment (= 7 days).



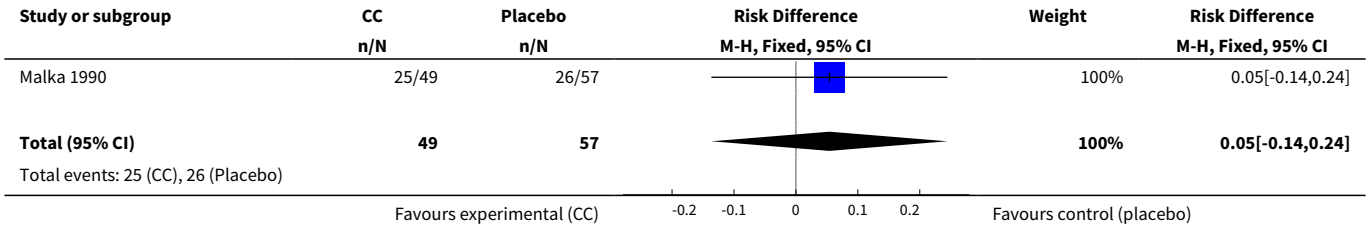
Analysis 8.2. Comparison 8 Expectoration (CC versus placebo), Outcome 2 Expectoration at the end of treatment (= 7 days).

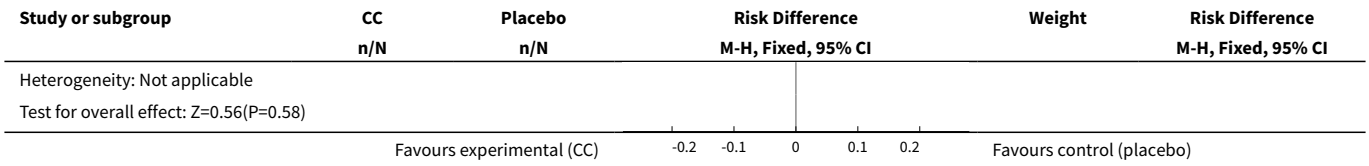


Comparison 9. Pulmonary function tests (CC versus placebo)

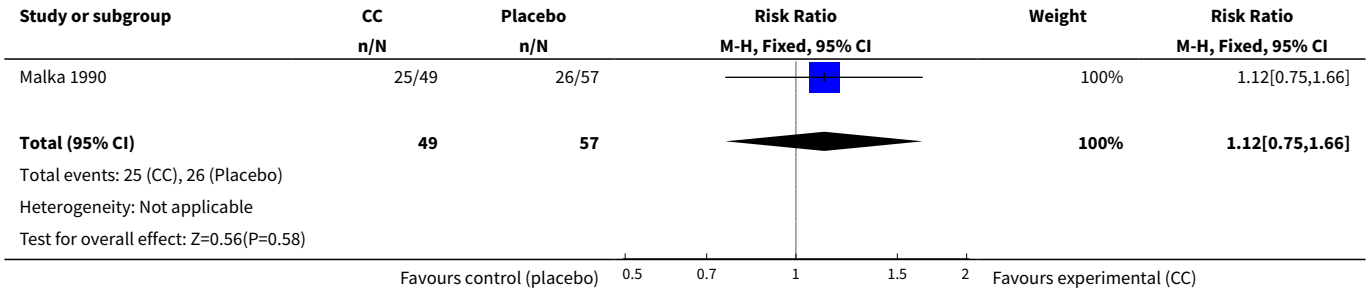
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Alteration of the pulmonary function after 3 days	1	106	Risk Difference (M-H, Fixed, 95% CI)	0.05 [-0.14, 0.24]
2 Alteration of the pulmonary function after 3 days	1	106	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.75, 1.66]

Analysis 9.1. Comparison 9 Pulmonary function tests (CC versus placebo), Outcome 1 Alteration of the pulmonary function after 3 days.





Analysis 9.2. Comparison 9 Pulmonary function tests (CC versus placebo), Outcome 2 Alteration of the pulmonary function after 3 days.



ADDITIONAL TABLES

Table 1. Characteristics of studies included to evaluate safety

Study	Methods	Participants	Intervention	Outcomes	Notes	Allocation concealment
Anonymous 1987	Case report	20 children (1 to 14 years)	Oral carbocysteine 300 mg/day above 5 years 200 mg/day under 5 years 2 to 3 times daily for 6 days (except 1: 3 days)	Clinical: cough frequency and intensity, sputum quality and quantity	French	Not used
Baldini 1989	RCT Active treatment (ambroxol); participants received antibiotics if necessary	28 children older than 2 years old	Oral acetylcysteine 300 mg/day above 5 years 200 mg/day under 5 years For 10 days	Clinical: expectoration, sputum viscosity, dyspnoea, cough, difficulty of expectoration. Biological: blood exam, monitoring of hepatic and renal function	Italian	Unclear
Banovcin 1990	Controlled trial Active treatment (Ipecac syrup); antibiotics and vitamins for all participants	18 children (6 to 15 years)	Oral carbocysteine 250 mg 3 times a day	PFT	Slovak	Unclear

Table 1. Characteristics of studies included to evaluate safety *(Continued)*

Banovcin 1992	RCT Active treatment (Ipecac syrup); antibiotics for all participants	51 children (6 to 24 months)	Oral carbocysteine 50 to 62.5 mg 3 times a day	Clinical score: lung auscultation, fever, cough Biological: blood exam	Slovak	Unclear
Bellomo 1967a	Controlled trial Control participants received no treatment	81 children (< 8 years)	Intramuscular acetylcysteine 25 to 50 mg/kg/day	Clinical: cough, dyspnoea, thoracic semeilogic alteration, fever	Italian	Unclear
Bellomo 1967b	Uncontrolled trial Thiamphenicol for all participants	39 children (16: < 2 years)	Intramuscular acetylcysteine 10 to 18 mg/kg/day	Clinical: cough, dyspnoea, thoracic semeilogic alteration, fever Biological: blood exam; X-ray	Italian	Unclear
Bellomo 1972	RCT All participants received thiamphenicol with or without acetylcysteine	59 children (22: < 1 year; 28: 1 to 5 years; 9: > 5 years)	Oral acetylcysteine 13.8 mg/kg/day 2 to 4 times daily for 6 to 7 days average (maximum 14 days)	Clinical: duration of febrile state, dyspnoea, thoracic semeiologic alterations, cough	Italian	Unclear
Bellomo 1973	RCT Oral and intramuscular acetylcysteine; thiamphenicol for all participants	50 children (35: < 2 years)	Oral and intramuscular acetylcysteine 300 mg/day under 2 years 600 mg/day above	Clinical: cough, dyspnoea, thoracic semeilogic alteration, fever	Italian	Unclear
Berni 1983	RCT Antibiotics if necessary	30 children (2 to 8 years)	Oral carbocysteine 200 to 300 mg	Clinical: cough, dyspnoea, expectoration	Italian	Unclear
Biscatti 1972	RCT All participants received some kind of antibiotic	50 children (29: < 2 years; 21: > 2 years)	Oral acetylcysteine 100 mg/day under 2 years 200 mg/day between 2 and 4 years 300 mg/day above 4 years for 6 days	Clinical: cough, dyspnoea, thoracic semeilogic alteration, temperature level Biological: ESR and leucocyte count	Italian Possibly not comparable treatment because various antibiotics were used	Unclear
Boner 1984	Uncontrolled trial Cefuroxime for all participants	60 children (4 to 12 years)	Intramuscular acetylcysteine 15 to 30 mg/kg/day	Clinical: temperature, cough, chest and abdomen pain, dyspnoea, wheezing Bacteriological: respiratory secretion cultures X-ray	English	Unclear
Camurri 1990	RCT Active treatment (bromhexine)	32 children (2 to 11 years)	Oral acetylcysteine 300 mg/day	Clinical: cough, dyspnoea, expectoration (difficulty, quantity and quality)	Italian	Unclear

Table 1. Characteristics of studies included to evaluate safety *(Continued)*

Caramia 1984	Uncontrolled trial Cefuroxime for all participants	40 children (4 months to 13 years)	Intramuscular acetylcysteine 20 to 30 mg/kg/day	Clinical: cough, temperature, sputum viscosity, intrinsic sputum characteristics Bacteriological: respiratory secretion cultures X-ray	English	Unclear
Careddu 1989	RCT Active treatment (nesosteine)	40 children (5 to12 years)	Oral carbocysteine 900 mg/day	Clinical: cough, dyspnoea, expectoration Biological: blood exam	Italian	Unclear
Castello 1979	Controlled trial Antibiotics if necessary	13 children (1 of 15 months + 12: 2 to 12 years)	Oral carbocysteine; 3 spoons/day (2% under 4 years; 5% above 4 years)	Clinical: monitoring; viscosimetry	Italian	Unclear
Chalumeau 2002	Targeted pharmacovigilance study	6 children (< 2 years)	19.5 to 34.6 mg/kg/day 3 received oral carbocysteine 3 received oral acetylcysteine	Clinical: cough, sputum viscosity	French	Not used
Dano 1971	Uncontrolled trial	37 children (5 to 17 years)	Inhaled acetylcysteine 2 ml 10% + 2 ml 20%	Clinical: monitoring; PFT	English	Unclear
Fiocchi 1989	RCT All participants received antibiotics if necessary	100 children (all > 2 years)	Oral acetylcysteine 20 mg/kg/day 3 times a day for 28 days	Clinical: cough, cough productivity and thoracic semeilogic alteration PFT	Italian Side effects: 2 participants vomiting in acetylcysteine group, with 1 drop-out	Unclear
Gaudier 1968	Uncontrolled trial	50 children (< 15 years)	Oral acetylcysteine; 2 spoons 2%/day	Clinical: monitoring (evolution of asthma)	French	Unclear
Ginocchi 1978	Uncontrolled trial Antibiotics in 33 children	44 children (2 months to 13 years)	Oral carbocysteine 2 spoons/day under 5 years; 3 spoons/day above	Clinical: cough, dyspnoea, expectoration, sputum viscosity Biological: blood exam	Italian	Unclear
Gusberti 1985	RCT Active treatment (acetylsalicylate of acetylcysteine 4%, 5 ml x 3)	40 children (4 months to 13 years)	Oral acetylcysteine 200 mg 3 times a day	Clinical: cough, dyspnoea, expectoration (difficulty, quantity and quality), temperature Biological: blood exam	Italian	Unclear
Henocq 1985	RCT Control participants received no treatment	50 children (1 month to 4 years)	Oral carbocysteine 5 ml 2% per 5 kg/day	IgA level	French	Unclear

Table 1. Characteristics of studies included to evaluate safety *(Continued)*

Jean 1982	Uncontrolled trial Thiamphenicol for all participants	29 children (< 10 years)	Inhaled acetylcysteine 200 mg/day under 3 months 400 mg/day above	Clinical: cough, dyspnoea, expectoration, sputum viscosity, temperature Bacteriological X-ray, PFT, bronchoscopy	French	Unclear
Leupold 1970	Uncontrolled trial	36 children (7 to 16 years)	Inhaled acetylcysteine 15 min: 18 participants at 20% and 18 participants at 10%	Clinical: monitoring PFT	German	Unclear
Loscialpo Ramundo 1968	Uncontrolled trial Thiamphenicol for all participants	84 children (2 to 12 years)	Inhaled acetylcysteine 1.5 ml 10% above 5 years 3 ml 10 % under (the first 5 days twice a day then once a day)	Clinical: cough, dyspnoea, fever Biological: blood exam X-ray	Italian	Unclear
Malka 1990	RCT All participants received antibiotics if necessary	106 children (all > 2 years); all participants received antibiotics if necessary	Oral carbocysteine; 200 mg/day under 5 years 300 mg/day above for 7 days	Clinical: cough, expectoration, bronchial congestion, dyspnoea PFT	French 9 participants with side effects (in the carbocysteine group: 2 nausea, 3 diarrhoea, 1 stomach pain; in the placebo group: 1 nausea, 2 stomach pain)	Unclear
Mayaud 1980	Uncontrolled trial Thiamphenicol for all participants	112 children (< 8 years; 33: < 1 year)	Oral and intramuscular acetylcysteine 50 mg/kg/day	Clinical: fever, expectoration (quality); Biological: blood exam Bacteriological: quality of sputum X-ray	French	Unclear
Michael 1986	Uncontrolled trial	374 children (mean: 5 years +/- 3)	Oral carbocysteine; 500 mg/day under 4 years 750 mg/day above	Clinical: cough, sputum viscosity, expectoration, breathing	German	Unclear
Nakayama 1977	RCT Patients received bronchodilators, antibiotics, antihistamine if previously treated	152 children (0 to 18 years)	Oral carbocysteine; 30 mg/kg/day (in 3 to 4 doses a day for 7 days)	Clinical: overall assessment, cough, stridor, expectoration PFT	French	Adequate

Table 1. Characteristics of studies included to evaluate safety *(Continued)*

Nikolic 1980	Uncontrolled trial	20 children (3 to 14 years)	Oral acetylcysteine 100 to 200 mg 3 times a day	Clinical PFT	English	Unclear
Ramenghi 1984	Uncontrolled trial Cefuroxim for all participants	20 children (10 months to 2 years)	Intramuscular acetylcysteine 15 mg/kg/day	Clinical: cough, rale, vesicular murmur, irritability, hypo-alimentation Biological: blood exam Bacteriological: on pharyngotracheal aspirate	English	Unclear
Santangelo 1985	Uncontrolled trial Cefuroxim for all participants	103 children (2 months to 11 years)	Intramuscular acetylcysteine; 20 to 30 mg/kg/day	Clinical: monitoring Bacteriological: secretion cultures; X-ray	English	Unclear
Trastotenojo 1984	Controlled trial Antibiotics and bronchodilator if necessary	60 children (2 months to 13 years)	Oral acetylcysteine 100 mg 3 times a day	Clinical: cough, dyspnoea, findings on auscultation; Biological: blood exam X-ray	English	Unclear
Zanini 1974	RCT In treatment group 15 children received antibiotics + 4 inhaled acetylcysteine; in control group 8 children received antibiotics	30 children (18 < 1 year; 12 > 1 year)	Oral carbocysteine from 100 to 400 mg/day depending on age for 5 to 9 days	Clinical: cough, dyspnoea, temperature level, appetite, general condition	Italian	Unclear

RCT: randomised controlled trial
PFT: pulmonary function tests
ESR: erythrocyte sedimentation rate

APPENDICES

Appendix 1. CENTRAL and MEDLINE search strategy

MEDLINE (Ovid)
1 exp Respiratory Tract Infections/
2 respiratory tract infection*.tw.
3 respiratory infection*.tw.
4 exp Rhinitis/
5 rhinit*.tw.
6 (rhinopharyngit* or nasopharyngit* or rhinosinusit* or nasosinusit*).tw.
7 Common Cold/
8 common cold*.tw.
9 Influenza, Human/
10 (influenza* or flu).tw.
11 Pharyngitis/
12 pharyngit*.tw.
13 exp Sinusitis/
14 sinusit*.tw.
15 exp Laryngitis/

16 laryngit*.tw.
17 Tracheitis/
18 tracheit*.tw.
19 tracheobronchit*.tw.
20 sore throat*.tw.
21 Cough/
22 cough*.tw.
23 exp Bronchitis/
24 exp Bronchiolitis/
25 (bronchiolit* or bronchit*).tw.
26 exp Pneumonia/
27 (pneumon* or bronchopneumon* or pleuropneumon* or broncho-pulmon*).tw.
28 or/1-27
29 Acetylcysteine/
30 acetylcysteine.tw,nm.
31 (n-acetylcysteine or n-acetyl-l-cysteine or acetyl-cysteine or nac).tw,nm.
32 Carbocysteine/
33 (carbocysteine or carbocisteine).tw,nm.
34 exp Expectorants/
35 expectorant*.tw.
36 mucolytic*.tw.
37 or/29-36
38 28 and 37

Appendix 2. EMBASE search strategy

41. #30 AND #40
40. #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39
39. 'nursery school':ab,ti OR 'primary school':ab,ti OR 'secondary school':ab,ti OR 'elementary school':ab,ti OR 'high school':ab,ti OR kindergar*:ab,ti OR highschool*:ab,ti
38. pediatric*:ab,ti OR paediatric*:ab,ti
37. 'pediatrics'/exp
36. adoles*:ab,ti OR teen*:ab,ti OR boy*:ab,ti OR girl*:ab,ti
35. 'adolescent'/exp
34. child*:ab,ti OR schoolchild*:ab,ti OR 'school age':ab,ti OR 'school aged':ab,ti OR preschool*:ab,ti OR kid:ab,ti OR kids:ab,ti OR toddler*:ab,ti
33. 'child'/exp
32. infant*:ab,ti OR infancy:ab,ti OR newborn*:ab,ti OR baby:ab,ti OR babies:ab,ti OR neonat*:ab,ti OR preterm*:ab,ti OR prematur*:ab,ti
31. 'infant'/exp
30. #20 AND #29
29. #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28
28. expectorant*:ab,ti
27. 'expectorant agent'/de
26. mucolytic*:ab,ti
25. 'mucolytic agent'/exp
24. carbocysteine:ab,ti OR carbocisteine:ab,ti
23. 'carbocisteine'/exp
22. acetylcysteine:ab,ti OR 'n-acetylcysteine':ab,ti OR 'n-acetyl-l-cysteine':ab,ti OR 'acetyl-cysteine':ab,ti OR nac:ab,ti
21. 'acetylcysteine'/de
20. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #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
19. bronchit*:ab,ti OR bronchiolit*:ab,ti
18. 'bronchitis'/exp
17. 'sore throat':ab,ti OR 'sore throats':ab,ti
16. 'sore throat'/de
15. laryngit*:ab,ti
14. 'laryngitis'/exp
13. sinusit*:ab,ti
12. 'sinusitis'/exp
11. pharyngit*:ab,ti
10. 'pharyngitis'/exp
9. influenza*:ab,ti

8. 'influenza'/exp
7. 'common cold':ab,ti OR 'common colds':ab,ti
6. 'common cold'/exp
5. rhinopharyngit*:ab,ti
4. rhinit*:ab,ti
3. 'rhinitis'/exp
2. 'respiratory tract infection':ab,ti OR 'respiratory tract infections':ab,ti OR 'respiratory infection':ab,ti OR 'respiratory infections':ab,ti
1. 'respiratory tract infection'/exp

Appendix 3. Web of Science search strategy

Topic=(respiratory infection* or respiratory tract infection* or rhinit* or rhinopharyngit* or common cold* or influenza* or pharyngit* or sinusit* or laryngit* or sore throat* or bronchit* or bronchiolit*) AND Topic=(acetylcysteine or n-acetyl-l-cysteine or acetyl-cysteine or nac or carbocysteine or carbocisteine or expectorant* or mucolytic*)

Refined by: Topic=(child* or infant* or infancy or newborn* or baby or babies or prematur* or preterm* or toddler* or preschool* or school age* or schoolchild* or nursery school* or primary school* or elementary school* or highschool* or high school* or kid or kids or adoles* or teen* or boy* or girl* or kindergar* or pediatric* or paediatric*)

Appendix 4. Previous CENTRAL and MEDLINE search strategy

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2007, Issue 4) which contains the Cochrane Acute Respiratory Infections (ARI) Group's Specialised Register; MEDLINE (1966 to March 2008); EMBASE (1980 to March 2008); Micromedex (April 2008); Pascal (1987 to 2004) and Science Citation Index (1974 to March 2008).

We used the following search terms to search MEDLINE and CENTRAL; we adapted these terms to search the other electronic databases.

MEDLINE (PubMed)
#1. Exp Acetylcysteine/
#2. acetylcysteine
#3. exp Carbocysteine/
#4. carbocysteine
#5. exp Expectorants/
#6. expectorant$
#7. exp Mucolytics/
#8. mucolytics
#9. 1-8 OR
#10. Exp Respiratory Tract Infections/
#11. respiratory tract infections
#12. respiratory infections
#13. exp Rhinitis/
#14. rhinitis
#15. exp Common Cold/
#16. common cold
#17. exp Influenza/
#18. influenza
#19. exp Pharyngitis/
#20. pharyngitis
#21. exp Sinusitis/
#22. sinusitis
#23. exp Laryngitis/
#24. laryngitis
#25. sore throat
#26. exp Bronchitis/
#27. bronchitis
#28. exp Bronchiolitis/
#29. bronchiolitis
#30. 10-29 OR
#31. Exp Child/
#32. child*
#33. paediatric*
#34. paediatric*

#35. 32-34 OR
#36. 9 AND 30 AND 35

FEEDBACK

Acetylcysteine and carbocysteine for acute upper and lower respiratory tract infections in paediatric patients without chronic broncho-pulmonary disease, 12 March 2013

Summary

Comment: I did not understand which criteria were selected to dertermine efficacy of acetylcysteine and carbocysteine drugs. Until now I thought they were of no interest in ARTI's and this article doesn't give me any point to change my point of view. Thank you for answer.

I agree with the conflict of interest statement below:
I certify that I have no affiliations with or involvement in any organization or entity with a financial interest in the subject matter of my feedback.

Reply

We have just finished updating our review which will published soon. The criteria selected to determine efficacy of acetylcysteine and carbocysteine drugs are included in the 'Types of outcome measures'. I have also copied our conclusions**:**

Types of outcome measures

We included trials reporting at least one of the following outcome measures.

Primary outcomes

1. Time to resolution of clinical symptoms and/or signs (where clinical symptoms and signs may include increased respiratory rate, use of accessory respiratory muscles, abnormal lung examination, cough, sputum production, fever, or activity limitations).

2. Proportions of patients with clinical symptoms and/or signs at a designated time.

3. Global assessment of improvement by clinicians, patients or their parents at a designated time.

Secondary outcomes

1. Reduced hospitalisation rates and/or duration of hospitalisation stay.

Authors' conclusions

The results have to be interpreted with caution because they are based on a limited number of participants included in studies whose methodological quality is questionable. Acetylcysteine and carbocysteine seem to have a limited efficacy and appear to be safe in children older than two years. These results should take into consideration the fact that acetylcysteine and carbocysteine are prescribed for self-limiting diseases (for example, acute cough, bronchitis). Given strong concerns about safety, these drugs should only be used for acute upper and lower RTIs in the context of a RCT with regards to children younger than two years.

Contributors

Martin Chalumeau
Yvonne Duijvestijn

WHAT'S NEW

Date	Event	Description
9 April 2013	Feedback has been incorporated	Feedback comment and reply added to the review.
6 March 2013	New citation required but conclusions have not changed	Searches conducted.
6 March 2013	New search has been performed	In this update, no new trials were identified for inclusion. We excluded one new trial (Varricchio 2008). The conclusions about the efficacy of the treatment remain unchanged. However, we found new literature supporting evidence for side effects of car-

Date	Event	Description
		bocysteine and acetylcysteine, which led to the withdrawal of the licence of carbocysteine and acetylcysteine in paediatric patients younger than two years in France in April 2010, and then in Italy. This has been added to the conclusions of this updated review.

HISTORY

Protocol first published: Issue 3, 2001
Review first published: Issue 1, 2009

Date	Event	Description
28 March 2008	New search has been performed	Searches conducted.
19 February 2008	Amended	Converted to new review format.
3 October 2006	New citation required but conclusions have not changed	A subgroup analysis of infants under two years old was added because of reports of paradoxical bronchial congestion and obstruction in infants under two years old receiving carbocysteine and acetylcysteine for acute cough.

CONTRIBUTIONS OF AUTHORS

Yvonne Duijvestijn (YD) participated in the writing of the protocol, then took the lead of the review, participated in the data collection and analysis, wrote the first draft of the review and participated in the update of the review.
Martin Chalumeau (MC) had the original idea for the study, wrote the first draft of the protocol, participated in data collection and analysis, in the writing of the review and wrote the first draft of the update.

DECLARATIONS OF INTEREST

No financial conflict of interest.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None.

INDEX TERMS

Medical Subject Headings (MeSH)

Acetylcysteine [adverse effects] [*therapeutic use]; Acute Disease; Age Factors; Carbocysteine [adverse effects] [*therapeutic use]; Cough [drug therapy]; Expectorants [adverse effects] [*therapeutic use]; Randomized Controlled Trials as Topic; Respiratory Tract Infections [*drug therapy]

MeSH check words

Child; Child, Preschool; Humans; Infant