Symptomatic treatment of the cough in whooping cough (Review)

Bettiol S, Wang K, Thompson MJ, Roberts NW, Perera R, Heneghan CJ, Harnden A

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[Intervention Review]

Symptomatic treatment of the cough in whooping cough

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ABSTRACT

Background

The worldwide incidence of whooping cough (pertussis) has been estimated at 48.5 million cases and nearly 295,000 deaths per year. In low-income countries, the case-fatality rate among infants may be as high as 4%. Much of the morbidity of whooping cough in children and adults is due to the effects of the paroxysmal cough. Cough treatments proposed include corticosteroids, beta 2-adrenergic agonists, pertussis-specific immunoglobulin, antihistamines and possibly leukotriene receptor antagonists (LTRAs).

Objectives

To assess the effectiveness and safety of interventions to reduce the severity of paroxysmal cough in whooping cough in children and adults.

Search methods

We updated searches of the Cochrane Central Register of Controlled Trials (CENTRAL Issue 2, 2012), which contains the Cochrane Acute Respiratory Infections Group's Specialised Register, the Database of Abstracts of Reviews of Effects (DARE Issue 2, 2012) accessed from *The Cochrane Library*, MEDLINE (1950 to January 2012), EMBASE (1980 to January 2012), AMED (1985 to January 2012), CINAHL (1980 to January 2012) and LILACS (January 2012). We searched Current Controlled Trials to identify trials in progress.

Selection criteria

We selected randomised controlled trials (RCTs) and quasi-RCTs of any intervention (excluding antibiotics and vaccines) to suppress the cough in whooping cough.

Data collection and analysis

Two review authors (SB, MT) independently selected trials, extracted data and assessed the quality of each trial for this review in 2009. Two review authors (SB, KW) independently reviewed additional studies identified by the updated search in 2012. The primary outcome was frequency of paroxysms of coughing. Secondary outcomes were frequency of vomiting, frequency of whoop, frequency of cyanosis (turning blue), development of serious complications, mortality from any cause, side effects due to medication, admission to hospital and duration of hospital stay.

Main results

Ten trials were included of varying sample sizes (N = 9 to 135) from high-income countries. Study quality was generally poor. Included studies did not show a statistically significant benefit for any of the interventions. Only six trials including a total of 196 participants reported data in sufficient detail for analysis. Diphenhydramine did not change coughing episodes; the mean difference (MD) of coughing spells per 24 hours was 1.9; 95% confidence interval (CI) - 4.7 to 8.5. One study on pertussis immunoglobulin reported a possible mean reduction of -3.1 whoops per 24 hours (95% CI -6.2 to 0.02) but no change in hospital stay (MD -0.7 days; 95% CI -3.8 to 2.4). Dexamethasone did not show a clear decrease in length of hospital stay (MD -3.5 days; 95% CI -15.3 to 8.4) and salbutamol showed no change in coughing paroxysms per 24 hours (MD -0.2; 95% CI -4.1 to 3.7). Only one trial comparing pertussis immunoglobulin versus placebo reported data on adverse events: 4.3% in the treatment group (rash) versus 5.3% in the placebo group (loose stools, pain and swelling at injection site).

Authors' conclusions

There is insufficient evidence to draw conclusions about the effectiveness of interventions for the cough in whooping cough.

PLAIN LANGUAGE SUMMARY

Treatment of the cough in whooping cough

Whooping cough, or pertussis, is an infectious bacterial disease. It affects infants and small children and can be life-threatening in unimmunised infants younger than three months of age. Infants with whooping cough experience severe bouts of coughing and vomiting which can lead to dehydration and difficulty breathing. Routine vaccination can prevent illness and protect infants and children against death and admission to hospital.

Whooping cough also affects older children and adults and new vaccine strategies are being developed to improve coverage, as neither immunisation nor natural infection result in lifelong immunity. New improved laboratory methods and higher awareness amongst doctors have helped improve surveillance of community outbreaks. These methods have also helped improve diagnosis as antibiotics can limit the course of the disease if given in the early stage of the illness. In the later stages, antibiotics have little individual benefit and treatment with corticosteroids, salbutamol, pertussis specific immunoglobulin (antibodies to increase the body's resistance) or antihistamines has been used in an attempt to reduce the cough while the disease runs its course.

We reviewed 10 studies involving children and adults with whooping cough. Only six of these studies, which included a total of 196 patients, reported their results in enough detail for us to assess them. The studies involved different types of interventions (excluding antibiotics and vaccines) and found that no trial provided enough evidence to determine whether the drugs used can reduce the cough in whooping cough. The risk of side effects was similar in patients treated with pertussis-specific immunoglobulin or placebo.

BACKGROUND

Description of the condition

Whooping cough, or pertussis, is a highly infectious disease caused by gram-negative coccobacillus *Bordetella pertussis (B. pertussis)*. The worldwide incidence of pertussis has been estimated to be 48.5 million cases per year, causing 295,000 deaths (Mattoo 2005; Tan 2005; WHO 2005a). The rate of case-fatality among infants in low-income countries may be as high as 4% (Tan 2005; WHO 2005b). There is evidence of a global resurgence in the incidence of pertussis and, with improved recognition, increasing reports of pertussis in adolescent and adult populations (CDC 2005; Cherry 2006; Dworkin 2005; Quinn 2007; Tan 2005). This means neonates and infants are particularly vulnerable to the possibility of disease transmitted by infectious adults in the community. Childhood immunisation has dramatically reduced the incidence of severe disease but the protection provided by childhood immunisation or natural infection is not lifelong. The World Health Organization (WHO) states that the approximate length of immunity is expected to be 10 years, although figures

are variable and immunity may range from six to 12 years (WHO 2005b); some have estimated immunity to be as low as four years after vaccination (Wendelboe 2005).

Clinically, pertussis is a prolonged disease and can be classically divided into catarrhal, paroxysmal and convalescent stages. The symptoms during the catarrhal stage are similar to a minor upper respiratory infection or head cold (coryza) with an intermittent non-productive cough commonly lasting one to two weeks, with possible fever. The paroxysmal phase is when coughing begins to occur in spells (paroxysms) that may last for over a minute. The gasping for air between coughing defines the characteristic inspiratory whoop, although infants may not whoop as older children do. Coughing paroxysms can also lead to post-tussive vomiting which may result in dehydration, especially in low-income countries (Long 2000).

Severe complications of the disease such as apnoea, cyanosis, pneumonia, seizures, encephalopathy and death can occur in young infants (Mattoo 2005; McEniery 2004; von König 2002). In such cases hospitalisation for supportive care or intensive care may be required. The severity of the paroxysmal phase usually peaks after one or more weeks and may persist for two or three months with an average of five coughing episodes a day before gradual improvement (Harnden 2006). Even without severe complications the coughing spasms are very distressing for the child and parents. The clinical manifestations of the disease are affected by several known factors, including the age of the patient, immunisation status or history of natural infection, presence of passively acquired antibody, and antibiotic treatment. While the disease stages are foreshortened in immunised children, pertussis can be a major cause of persistent cough. A study in the UK found that 37% of school children who were coughing for more than two weeks had evidence of a recent infection (Harnden 2006).

In adults the clinical presentation can range from no cough to mild or 'classic pertussis' which includes the characteristic whoop, possible post-tussive vomiting or a prolonged cough illness (Hewlett 2005; Wright 1995). Other reported complications include urinary incontinence (Postels-Multani 1995), hearing loss, inguinal hernia, cracked ribs, carotid artery dissection and pneumonia (Rothstein 2005). These complications can have social and economic implications resulting in the individual being absent from work or school and requiring frequent use of healthcare resources (Rothstein 2005).

Diagnosis of infection in the older population is important for treatment and surveillance purposes, but also to prevent transmission to unvaccinated babies. Recent advances in laboratory diagnostic methods have rapidly evolved from the less sensitive techniques such as culture and antigen detection to polymerase chain reaction (PCR), and the more sensitive antibody detection in serum and oral fluid against pertussis toxin (PT) (Litt 2006). These advances have contributed to rapid and reliable identification which help with treatment and control measures.

The current global increase of pertussis and growing awareness of the implications in older populations have led to new strategies in improving vaccine coverage. Many countries, like the UK, have changed from the whole cell vaccine to the acellular vaccine. Vaccine regimes have also been extended in some countries to include pre-school and adolescent boosters as well as incorporating the 'cocoon strategy' that aims to ensure vaccine coverage of adolescents, adults and postpartum women (Forsyth 2005; Ward 2005); a strategy currently implemented in Australia and parts of the USA. Overall, much effort has been placed on standardising case definitions of surveillance and outbreak investigations. Diagnostic methods are advancing and considerable progress has been made in improving the understanding of pertussis even at the molecular level (King 2008). There are difficulties for those in low-income countries where these tools may not be available. The current challenge is assisting those that suffer from the consequences of this disease.

Description of the intervention

Treatment options depend on the stage of disease. In the early stages options are fairly standard and the preferred agents include a short treatment of macrolide antibiotics such as azithromycin or erythromycin (Altunaiji 2011). In later stages antibiotics have no effect on the clinical symptoms or course of pertussis but are prescribed primarily to eradicate *B. pertussis* from the nasopharynx and to limit the spread of infection rather than for individual benefit (Altunaiji 2011).

Much of the morbidity of whooping cough is due to the effects of the paroxysmal cough. The treatment of the cough is symptomatic, that is, treatment aims to reduce the severity of the cough paroxysms until the disease has run its course (Long 2000), but the value of current interventions used to relieve the ongoing symptoms is limited. The treatments that have been recommended include corticosteroids (for example, dexamethasone), salbutamol (beta 2-adrenergic stimulant), pertussis-specific immunoglobulin and antihistamines (for example, diphenhydramine). Expert opinion suggests leukotriene receptor antagonist (LTRA) may have some benefit, but current data are limited (Chang 2011).

How the intervention might work

Corticosteroids, such as dexamethasone, are synthetic adrenocortical steroids. These drugs alter the body's natural defensive response, reduce symptoms such as swelling and allergic-type reactions, and are often used to treat different kinds of inflammation. Salbutamol is a beta2-adrenergic agonist widely used for the relief of bronchospasm in conditions such as asthma and chronic obstructive pulmonary disease. There are a number of different types of antihistamine medicines available that are classified as either first generation or second generation, the difference being that the latter cause less drowsiness. Antihistamines work by blocking the

effects of the protein histamine produced by the body to protect it from infection. Inflammation of the airways that often leads to symptoms of sneezing or coughing can be reduced by their use. Pertussis immunoglobulin products are therapies directed at pertussis toxin, the major virulence factor of *B. pertussis*. LTRA is a hormone antagonist acting upon leukotrienes or natural mediators considered responsible for the effects of an inflammatory response similar to the process of histamine production. Leukotrienes also have a powerful effect in bronchoconstriction and increase vascular permeability, and are currently used in the treatment of asthma.

Why it is important to do this review

Specific treatments for the underlying cause of cough should ideally reduce or eliminate it. Unfortunately, in the case of pertussis, apart from early antibiotic intervention there are no disease-specific therapies available that can relieve the progressive nature of the cough. The paroxysmal stage of pertussis can be life-threatening for young infants and distressing for both child and parent. In adults this coughing phase can continue for several weeks, and can be uncomfortable and distressing.

To date there has been no significant evidence of benefit for any individual treatment in reducing the symptoms and morbidity associated with whooping cough.

OBJECTIVES

To evaluate the effectiveness of interventions to reduce the severity of the coughing paroxysms in whooping cough in children and adults.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) and quasi-RCTs comparing the effects of interventions to reduce the severity of coughing paroxysms in whooping cough.

Types of participants

We included trials of children and adults with whooping cough (as diagnosed by the trial authors) in any setting.

Types of interventions

We included any intervention (excluding vaccines and antibiotics) aimed at reducing the severity of the coughing paroxysms in whooping cough compared to another treatment for cough (if treatment has also been compared to placebo or no treatment in the same or another trial), placebo or no treatment.

Types of outcome measures

Primary outcomes

1. Frequency of paroxysms of coughing.

Secondary outcomes

1. Frequency of vomiting.
2. Frequency of whoop.
3. Frequency of cyanosis (turning blue) during cough.
4. Development of a serious complication, for example cerebral haemorrhage or convulsions; or presence of subcutaneous emphysema or pneumothorax.
5. Mortality from any cause.
6. Side effects of medication (as defined by authors of identified trials).
7. Admission to hospital.
8. Duration of hospital stay.

Search methods for identification of studies

Electronic searches

We updated searches of the Cochrane Central Register of Controlled Trials (CENTRAL) Issue 2, 2012, part of *The Cochrane Library,* www.thecochranelibrary.com (accessed 12 January 2012), which contains the Cochrane Acute Respiratory Infections Group's Specialised Register, the Database of Abstracts of Reviews of Effects (DARE) 2012, Issue 2 (accessed 12 January 2012 from *T he Cochrane Library*), MEDLINE (1950 to January 2012), EMBASE (1980 to January 2012), AMED (1985 to January 2012), CINAHL (1980 to January 2012) and LILACS (January 2012). We searched for studies published in languages other than English and ongoing trials in Current Controlled Trials (http://controlled-trials.com/).

We developed a search strategy for use in MEDLINE and revised it accordingly for other databases. We combined the search strategy with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity-maximising version (2008 revision) (Lefebvre 2011). Randomised controlled trial (RCT) filters applied to EMBASE were according to Ovid Clinical Queries: treatment (two or more terms high sensitivity)

(Wong 2006a); RCT filters applied to CINAHL were according to EbscoHOST Clinical Queries: Therapy - High Sensitivity (Wong 2006b); and RCT filters applied to LILACS were according to Manríquez 2008.

See Appendix 1, Appendix 2, Appendix 3 and Appendix 4 for the EMBASE, CINAHL, AMED and LILACS search strings.

MEDLINE (OVID)

1. Whooping Cough/
2. Bordetella pertussis/
3. (whoop* or pertus*).tw.
4. 1 or 2 or 3
5. exp Vaccines/
6. exp Anti-Bacterial Agents/
7. 6 or 5
8. 4 not 7
9. Albuterol/
10. (salbutamol or albuterol or ventmax or ventolin or volmax or airomir or asmasal or salamol or salbulin).tw
11. beta agonist*.tw.
12. Adrenergic beta-Agonists/
13. Bronchodilator Agents/
14. exp "Nebulizers and Vaporizers"/
15. (inhaler* or nebuliser* or nebulizer* or bronchodilator* or vaporiser* or vaporizer*).tw.
16. exp Adrenal Cortex Hormones/
17. exp Steroids/
18. (steroid* or corticosteroid* or corticoid* or glucocorticoid* or cortison* or prednisone or prednisolone or hydrocortisone).tw.
19. exp Expectorants/
20. (mucolytic* or carbocisteine or erdosteine or erdotin or mecysteine or methyl cysteine or visclair or mucoactive).tw.
21. (cough adj5 suppress*).tw.
22. exp Antitussive Agents/
23. (antitussive or anti tussive or protussive or pro tussive).tw.
24. codeine.tw.
25. (cough adj5 (remed* or therap* or treatment* or management or medicine* or medication*).tw.
26. (pholocodine or dextromethorphan or linctus).tw.
27. (demulcent* or ipecacauanha or expectorant*).tw.
28. (decongestant* or ephedrine or oxymetazoline or phenylephrine or pseudoephrine or xylometazoline).tw.
29. (sudafed or galpseud or galenphol or benylin or calpol or tixulix or robitussin or galsud or actifed or vicks).tw.
30. exp Histamine Antagonists/
31. (benadryl or diphenhydramide or promethazine or brompheniramine or chlorphenamine or doxylamine or triprolidine or chlorphenizamine or phenergan or piriton or anti histamine* or antihistamin* or histamine antagonist*).tw.
32. Honey/
33. exp Glycerol/
34. Zinc/
35. (honey or glycerol or zinc or glycerin).tw.
36. exp "Hypnotics and Sedatives"/
37. (sedat* or diazepam or phenobarbitone or phenobarbitol or chlorpromazine or largactil).tw.
38. exp Cholinergic Antagonists/
39. (anticholinergic adj (drug or agent* or therap*)).tw.
40. cholinergic antagonist*.tw.
41. levodropropizine.tw.
42. ipratropium bromide.tw.
43. moguisteine.tw.
44. or/9-43
45. 4 and 44
46. randomized controlled trial.pt.
47. controlled clinical trial.pt.
48. randomized.ab.
49. placebo.ab.
50. drug therapy.fs.
51. randomly.ab.
52. trial.ab.
53. groups.ab.
54. 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53
55. (animals not (humans and animals)).sh.
56. 54 not 55
57. 8 and 56
58. 56 and 45
59. 57 or 58

Searching other resources

We reviewed reference lists of eligible trials and previous systematic reviews generated by the searches outlined. We attempted to identify all relevant trials irrespective of language and publication status. We assessed non-English language papers through selective translation by a native speaker where possible and conducted translations of full texts where it was deemed necessary. We scanned reference lists of identified articles, conference abstracts, grey literature and pharmaceutical companies for additional published and unpublished trials.

Data collection and analysis

Selection of studies

Two review authors (SB, MT) independently screened the results of the literature search and selected eligible trials according to our preset criteria.

Data extraction and management

One review author (SB) entered data into RevMan 2011. A second review author (KW) checked the entered data. We extracted the following data from each trial: participants (age and gender), criteria used to diagnose whooping cough and type of intervention and outcomes, including side effects.

Assessment of risk of bias in included studies

Two review authors (SB, MT) independently extracted methodological information from selected papers for the assessment of internal validity. We assessed the quality of trials according to random sequence generation (selection bias), allocation concealment (selection bias), blinding (performance bias and detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) and other bias. These were reported individually and not as a score. We contacted trial authors for additional information on data that were unclear or not reported. We resolved review author differences by discussion.

Measures of treatment effect

We obtained means and standard deviations using standard methods for accumulated data where possible. We expressed the effects as mean differences (MD) with 95% confidence intervals (CIs).

Unit of analysis issues

We analysed the single small, cross-over trial (Krantz 1985) as if it was a parallel-group trial.

Dealing with missing data

We attempted to contact the trial authors for additional information if data from the trial reports were unclear or missing.

Assessment of heterogeneity

We conducted a test of heterogeneity for each outcome. We examined heterogeneity amongst studies with the Chi^2 test to (significance was set at $P < 0.05$) and I^2 statistic (Higgins 2003). We considered other sources of heterogeneity, apart from differences in interventions, namely clinical diversity (children/adults and different dosages) and study quality.

Assessment of reporting biases

We assessed reporting biases using funnel plots where we had sufficient trials and considered reasons for asymmetry if it was noted.

Data synthesis

Where no heterogeneity was detected, we performed a random-effects meta-analysis. It was likely that these pooled estimates would be more conservative than those obtained using a fixed-effect model. Where substantial heterogeneity (I^2 statistic above 50%) was detected, we considered possible explanations for this and considered not combining results. Where necessary, we used sensitivity analysis to investigate the contribution of individual trials to any heterogeneity.

Subgroup analysis and investigation of heterogeneity

We planned subgroup analyses for the following factors.

1. Dosage, if different doses of the same drug were studied, to compare effectiveness of different doses of the same drug.
2. Age (under 12 months, 12 months to five years and over five years), as the severity of clinical features changes with age, thus participants' reactions to treatment may vary.
3. Whooping cough diagnosed bacteriologically or clinically, to compare the effectiveness of treatment in participants with proven and suspected whooping cough.
4. Severity of cough (treated in hospital (more severe) versus ambulatory care (less severe)), to compare how participants with different disease severities respond to treatment.

Sensitivity analysis

We planned a sensitivity analysis excluding poorer quality trials (unknown/inadequate allocation concealment or quasi-random allocation), if a sufficient number of trials of the same treatment was identified.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

See the 'Characteristics of included studies' and 'Characteristics of excluded studies' tables.

Results of the search

Our electronic literature searches produced a total of 1680 hits (without removing duplicates), i.e. 628 from MEDLINE, 275 from CENTRAL, 622 from EMBASE, three from LILACS, 60 from AMED and 92 from CINAHL. Removing duplicates resulted in 1367 hits. Twenty-six potentially eligible trials were identified after screening the abstracts and titles. We identified an additional three eligible trials after scanning the reference lists of full-

text papers. Ten trials were eligible for inclusion following our inclusion criteria. We did not identify any new trials for inclusion or exclusion in this 2012 update.

Included studies

Ten trials met the inclusion criteria (see the 'Characteristics of included studies' table) on the basis of published data only (Danzon 1988; Granstrom 1991; Halperin 2007; Krantz 1985; Lucchesi 1949; Mertsola 1986; Miraglia 1984; Pavesio 1977; Roberts 1992; Zoumboulakis 1973).

In three trials, whooping cough was diagnosed bacteriologically, five clinically, and two both bacteriologically and clinically. Reports were generally old with the earliest study being published in 1949, three in the 1970s, four in the 1980s, two in the 1990s, with the most recent published in 2007. Studies were performed in high-income countries, namely Greece, Finland and New Zealand and two trials each were from Canada, Italy and Sweden.

Interventions in the trials included antihistamines, pertussis immunoglobulin, corticosteroids and salbutamol. Sufficient data were extractable from only five trials. Several trial authors were contacted for additional information by the previous review authors (Pillay 2003), with one response received. We contacted one trial author for more information during this update and the data required were promptly provided.

Excluded studies

We reviewed the full-text versions of 15 studies, which were not included in this review. In six studies treatment was not randomly allocated (Ames 1953; Balagtas 1971; Bertaggia 1972; Eichlseder 1963; Pavesio 1979; Torre 1993). In five studies, the method used to allocate treatment was unclear (Brunskill 1986; Chandra 1972; Giuliani 1966; Musso 1982; Sacchetti 1982). One study did not include a comparator group for the intervention studied (Bruss 1999). In three studies details of the treatment given to the comparator group were unclear (Badr-El-Din 1976; Leen 1989; Lewis 1984). Details of these excluded studies are presented in the Characteristics of excluded studies table.

Risk of bias in included studies

Often trial methods would use the word 'random' and 'double-blinded' but did not describe the generation of the random sequence or who was blinded. Of the 10 included trials, two were quasi-RCTs, seven were RCTs (four with method of randomisation not stated) and one was a cross-over trial. Allocation concealment was clearly adequate in two trials (Danzon 1988; Halperin 2007), not stated in three (Lucchesi 1949; Pavesio 1977; Zoumboulakis 1973) and unclear in five (Granstrom 1991; Krantz 1985; Mertsola 1986; Miraglia 1984; Roberts 1992). Two trials were double-blinded (Danzon 1988; Halperin 2007); the remaining trials were inadequately described. Three trials included all patients in the final analysis; two had greater than 90% of the patients, one had 53% of the patients, and in three loss to follow-up was unclear. Intention-to-treat (ITT) analysis was reported in only one of the 10 trials (see the Characteristics of included studies table). The quality of reporting of methods was poor in most trials. The overall risk of bias is presented graphically in Figure 1 and summarised in Figure 2.

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

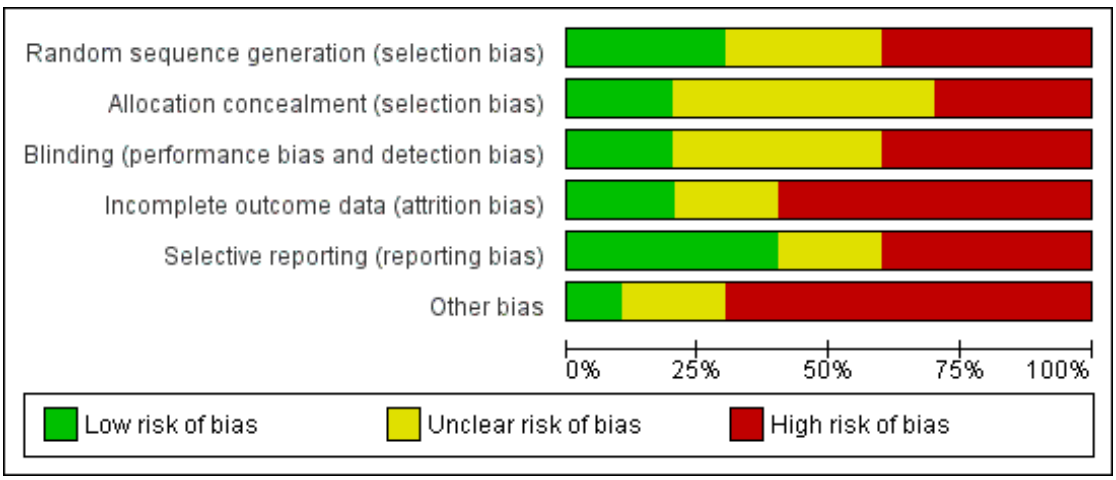
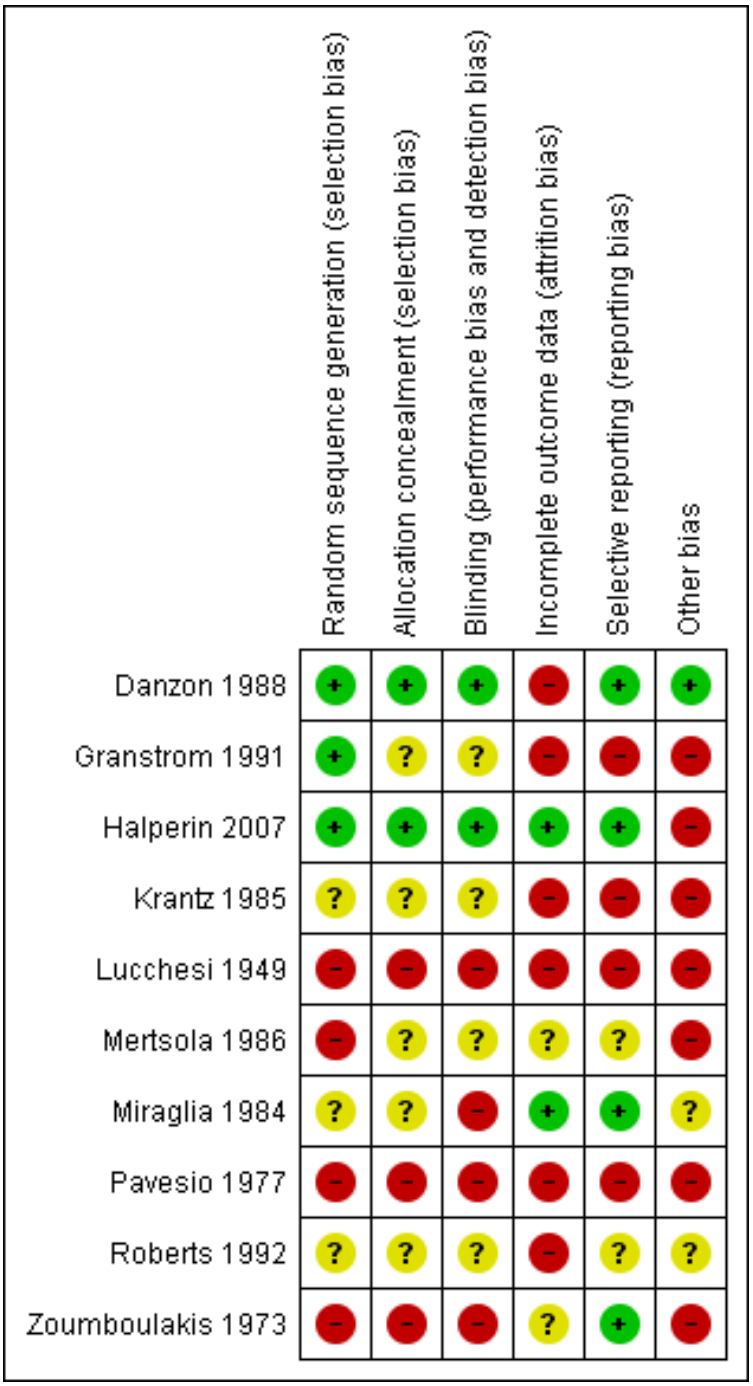


Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Allocation

In two trials the treatment assignment was adequately concealed prior to allocation (Danzon 1988; Halperin 2007) but was unclear or not available in the remaining eight trials.

Blinding

Two trials were deemed to be double-blinded trials (Danzon 1988; Halperin 2007). The majority were stated to be blinded but insufficient details were given to suggest whether the participants, outcome assessors or personnel were blinded. Three trials were not found to be blinded.

Incomplete outcome data

Two trials included data of all study participants in their results (Halperin 2007; Miraglia 1984). For the remaining trials either there was not enough information available to determine adequate outcome data or there was a difference in the proportion of incomplete outcome data across groups.

Selective reporting

The majority of trials had inadequate details in their protocol, or data were not reported in a way to assess this.

Other potential sources of bias

The process of assessing and measuring outcomes was variable amongst the trials. The scoring of whoops and coughs was not standard and more often subjective and dependent on different scoring systems.

Effects of interventions

We extracted data for pre-specified outcomes from 10 trials but sufficient data for further analysis were available in only six of these trials. Data were presented as mean and standard deviations in the reporting of trials. For the remainder of the trials (Lucchesi 1949; Miraglia 1984; Pavesio 1977; Zoumboulakis 1973) we listed the summary statistics reported by the trial authors for our pre-specified outcomes (Table 1), as authors either did not respond or were unable to provide requested data. Suitable data were available for the following interventions.

Antihistamines versus placebo

Danzon (Danzon 1988) conducted the only trial for the antihistamine diphenhydramine (N = 49) administered orally (5 mg/kg/day) in three doses. There was no statistically significant difference in coughing paroxysms, mean difference of 1.90 fewer coughs per 24 hours in the placebo group (95% CI -4.7 to 8.5; P = 0.66) (Analysis 1.1). Side effects were not reported.

Pertussis immunoglobulin versus placebo

Granstrom (Granstrom 1991) conducted a trial (N = 67) assessing the effect of two forms of immunoglobulins (mono-component toxoid pertussis vaccine and a two-component acellular pertussis vaccine). Sample groups were divided to receive either immunoglobulin or placebo and treatment was administered intramuscularly (8 ml). There was no statistically significant difference in the mean number of whoops per day, mean difference (MD) between the treatment and control groups -3.1 per day (95% CI -6.2 to 0.02; P = 0.66) (Analysis 2.2). However, this figure could suggest some indication of a potential effect. There was no statistically significant difference in the duration of hospital stay, MD -0.7 days in the treatment group (95% CI -3.8 to 2.4; P = 0.66) (Analysis 2.1). Side effects reported included rash in 4.3% of the treatment group together with loose stools, and pain and swelling at the injection site in 5.3% of the placebo group.

Halperin (Halperin 2007) conducted a multicentre RCT (N = 25) assessing the effect of intravenous pertussis immune globulin intravenous (P-IGIV). This preparation was administered as a single intravenous infusion initially at 1.5 ml/kg/hour, increasing gradually to 6.0 ml/kg/hour over three hours. The rate was decreased if there were any adverse events encountered. There was no statistically significant difference in paroxysmal cough in the treatment group as compared to the placebo group, MD -0.07 coughs per hour (95% CI -0.42 to 0.27; P = 0.65) nor were there any significant differences in whoops per hour in the immunoglobulin group as compared to the placebo group, MD -0.06 whoops per hour (95% CI -0.34 to 0.21; P = 0.65) (Analysis 2.3). P-IGIV was well tolerated by study participants with no infusion-related adverse events. Any adverse events reported were attributed to the disease or intercurrent-related infection. This study was terminated prematurely due to expiration of P-IGIV lots and unavailability of additional study product.

Corticosteroids versus placebo

One study (Roberts 1992) (N = 11) assessed the effect of dexamethasone on the duration of hospital stay. Treatment was administered orally at 0.3 mg/kg for four days. There was no statistically significant difference in duration of hospital stay, with a MD -3.5 days in the dexamethasone group (95% CI -15.3 to 8.4; P = 0.57) (Analysis 3.1). Side effects were not reported.

Salbutamol versus placebo

One study conducted with salbutamol was a cross-over trial (N = 17) (Krantz 1985). The dosage of salbutamol was 0.6 mg/kg/day in four divided doses for two days. There was no statistically significant difference in coughing paroxysms, mean increase of 0.3 coughs per 24 hours in the salbutamol group (95% CI -5.3 to 6). In the second study (Mertsola 1986) (N = 27) treatment was administered orally at 0.1 mg/kg three times a day for 10 days. There was no statistically significant difference in coughing paroxysms, MD -0.7 coughs per day in the salbutamol group (95% CI -6.2 to 4.7).

In both trials, data were reported for each 24-hour period. There was no evidence of heterogeneity in paroxysmal cough per 24 hours (P = 0.79). There was no statistically significant difference in coughing paroxysms, MD -0.22 coughs per 24 hours in groups treated with salbutamol (95% CI -4.1 to 3.7, P = 0.91) (Analysis 4.1). Side effects were not reported for either intervention.

DISCUSSION

Summary of main results

This systematic review examining the symptomatic treatment of whooping cough has found that there is insufficient evidence to support the use of current interventions. Only one trial indicated some benefit in the use of pertussis immunoglobulin but more research is required.

Overall completeness and applicability of evidence

For the 2009 review we updated the earlier search strategy (Pillay 2003; Appendix 5) by including all treatment terms and interventions associated with whooping cough before excluding terms such as antibiotics and vaccines. Antibiotic and vaccine reviews have been performed for these interventions. A Cochrane Review on antibiotic treatment in whooping cough has been published (Altunaiji 2011) and the previously withdrawn Cochrane Review on acellular vaccines for preventing whooping cough in children (Tinnion 2001) has been updated by a new team of authors (Zhang 2009). In 2009 we added one included trial to the previous review published in 2003 (Pillay 2003). We did not identify any new studies to include when we updated our searches in 2012.

No statistically significant effects were found for any of the interventions (except a borderline significant effect of pertussis immunoglobulin treatment on the mean number of whoops). Pertussis immunoglobulin (Granstrom 1991) could plausibly result in a decrease in the mean number of whoops by anything from 6.22 over 24 hours to an increase of 0.02 over 24 hours. For all the other interventions sample sizes were small and confidence intervals for the mean differences were wide. This indicates that there is insufficient evidence to reach any conclusion regarding their effectiveness. The pre-specified subgroup and sensitivity analyses were not feasible because of the small number of trials identified.

Quality of the evidence

Ten trials from our literature search between 1950 and 2012 met our inclusion criteria. Most of the trials were generally old and poorly reported while the majority of randomised controlled trials (RCTs) were performed in the 1980s. This partially explains the poor quality and inconclusive nature of the trials. There was one exception (Halperin 2007), which was well designed and well executed.

Potential biases in the review process

There were several key limitations to the included trials. The trials were too heterogenous in regards to their interventions and outcomes to allow pooling of results. The trials varied greatly in dose regimes and duration of treatment. There was inconsistency in measuring outcomes and the timing of those intervals. The outcome data were also presented differently, that is, frequency of whoops per hour or duration of symptoms. Methods of monitoring coughs were variable but expected to be due to the year of publication. The later trials were likely to include the recording of the progressive cough with monitors and digital equipment. Age and sex of children/participants enrolled in the trials were not always mentioned and only one study included children over 12 years of age and adults (Mertsola 1986). Immunisation status and antibiotic treatments were not always stated. In the majority of trials children were given antibiotics prior to intervention.

Fifteen trials were excluded from this review. These trials might have provided some useful information but the many methodological errors, including poor quality methods or analysis, problems with recruitment, time frame and allocation of patients and non-interpretable results, lead to several forms of bias and misleading conclusions. In some of the excluded trials the trial authors concluded that their work was more of a pilot study and more research on their intervention was recommended.

No trials of cough suppressants (for example, codeine) were identified. This may be due to trials on cough suppressants, bronchodilators and cough syrups not necessarily having been performed with reference to whooping cough. No current trials were identified for leukotriene receptor antagonists for cough in patients with whooping cough.

Agreements and disagreements with other studies or reviews

Throughout much of the literature we report a lack of controlled trials and contradictory reports for cough relief in whooping cough. No strong evidence exists of any treatment that can relieve the serious cough caused by whooping cough, although there was one study that found some evidence that pertussis immunoglobulin preparations might help. There are many short single-blinded trials, clinical observations and 'personal impressions' that discuss promising results for patients and may indeed hold some credit. However, well designed, placebo-controlled, double-blind trials of potential agents and or combinations are lacking and such trials need to be initiated for those with pertussis in a similar way that trials of therapies for croup and asthma have been performed in the past two decades. This void in new therapies for cough is not limited to those suffering from pertussis but is a general problem for treating coughs of various causes. Chung 2009 has noted that new therapies for cough are lacking while in several countries there are growing concerns about the safety and efficacy of commonly used cough medicines (MHRA 2009). Overall there is a need for new, effective antitussive drugs for patients with whooping cough.

AUTHORS' CONCLUSIONS

Implications for practice

Given the uncertain effectiveness and potential side effects of interventions for the cough in whooping cough, there appears to be no justification for their use.

Implications for research

Given the growing prevalence of pertussis in infants, adolescents and adults, there is an urgent need for large, well designed RCTs in whooping cough and symptom relief. More importantly, good quality, well reported RCTs of adequate statistical power are required. Well designed trials are required and the design should follow CONSORT (Consolidated Standards of Reporting Trials) (www.consort-statement.org) guidelines. CONSORT comprises a checklist and flow diagram to help improve the quality of reports of RCTs. The checklist includes descriptions of the randomisation procedure (allocation concealment), the mechanisms of blinding, number of people lost during the follow-up and some details about the analysis made.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Danzon 1988

Methods	Randomly allocated (table of random numbers controlled by the pharmacy) unknown to the investigator. Performed in a double-blinded pattern. Intention-to-treat analysis was not reported. Loss to follow-up was unclear
Participants	49 inpatients (gender not specified) under 1 year of age. Vaccination status and previous antibiotic treatment was not reported. Bacteriologically diagnosed pertussis
Interventions	Diphenhydramine 5 mg/kg/day orally in 3 doses
Outcomes	Average number of paroxysms of cough over 24 hours (between 25th and 48th hour after starting treatment)
Notes	Coughs monitored with microphones

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Table of random numbers
Allocation concealment (selection bias)	Low risk	Control allocation with double-blind pattern
Blinding (performance bias and detection bias) All outcomes	Low risk	Appearance, smell and taste of active drug and placebo syrups were similar. Coughs monitored around the clock with sets of microphones
Incomplete outcome data (attrition bias) All outcomes	High risk	-
Selective reporting (reporting bias)	Low risk	Report pre-specified study outcome
Other bias	Low risk	-

Granstrom 1991

Methods	Randomisation done by a computer generated table of random numbers. A double-blinded, placebo-controlled trial. Intention-to-treat analysis was not reported. 91.8% follow-up
Participants	Both male and female inpatients, age range 1.1 to 32.3 months. 51% of the patients had previous antibiotic treatment but were not previously vaccinated. Clinical, bacteriological or serological diagnosed pertussis
Interventions	Specific immunoglobulin treatment, 8 ml intramuscularly injected into the buttocks, 2 ml either side on the first day of admission and the next dose as soon as possible after the first injection or on the second day
Outcomes	Duration of paroxysms, vomiting, whoop and hospital stay, mean number of paroxysms. Noted by nurse and parental reports
Notes	None of the children had been immunised. Supportive therapy was provided including erythromycin and salbutamol

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer program of random numbers
Allocation concealment (selection bias)	Unclear risk	-
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Placebo solution of 20% human albumin administered. Unclear if outcome assessors were blinded. States it is 'double-blinded'
Incomplete outcome data (attrition bias) All outcomes	High risk	67 children randomised of whom only 47 met the inclusion criteria of cough $\leq$ 14 days
Selective reporting (reporting bias)	High risk	Incomplete reporting of outcomes of interest. The 2 different immunoglobulin groups were aggregated
Other bias	High risk	Insufficient sample size. Numerous potential confounders

Halperin 2007

Methods	Randomisation allocated by a computer-generated list in a 2:1 ratio with a balanced block size of 6 stratified by age and centre. Double-blinded, placebo-controlled. Intention-to-treat analysis was reported
Participants	25 infants < 5 years of age (17 P-IGIV, 8 placebo). Mean age 2.3 months in P-IGIV group and 19 months in the placebo group. 4 of the P-IGIV recipients and no placebo recipients received any doses of pertussis vaccine. 6 placebo and 12 P-IGIV recipients had laboratory confirmation of pertussis. Criteria for inclusion clearly outlined
Interventions	P-IGIV (750 mg/kg) or placebo was administered as a single infusion over 3 hours; initial infusion was 1.5 ml/kg/hr increasing gradually to 6.0 ml/kg/hr
Outcomes	Percentage of paroxysmal cough, vomiting, whoop, apnoea, cyanosis and nasal congestion. Mean slope and median events paroxysmal cough, oxygen desaturation, bradycardia, whoop and apnoea. Percentage reduction in paroxysms of cough between baseline and post-treatment period (48 hours), duration of hospital stay
Notes	Participants were monitored with a Physiac monitor designed for physiological variables for extended periods. Microphone recorded coughs

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Complete generated list
Allocation concealment (selection bias)	Low risk	Centrally
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants, personnel and assessor were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	-
Selective reporting (reporting bias)	Low risk	-
Other bias	High risk	Prematurely terminated due to poor recruitment and out of date product. Only 17 intervention and 8 control. Inadequate for planned study

Krantz 1985

Methods	Generation of randomisation sequence before cross-over point not reported. Double-blinded, placebo-controlled, cross-over study. Assessor (investigator) was blinded. Intention-to-treat analysis was not reported. 52.9% follow-up
Participants	21 participants, 9 evaluated. Hospitalised for young age and social reasons. Both male and female inpatients, age range 0.1 to 2.3 years of age. Vaccination status and previous antibiotic treatment was not reported. Patients had not been given salbutamol within 2 days of entering the trial and all had bacteriological or serological confirmed diagnosis of pertussis
Interventions	Salbutamol 0.6 mg/kg/day orally in 4 doses for 2 days
Outcomes	Number of paroxysms of cough, duration of paroxysms
Notes	Patients given erythromycin 25 mg/kg twice a day

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomly allocated sequence
Allocation concealment (selection bias)	Unclear risk	-
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Placebo syrup identical to active drug. Personnel blinded. Cross-over point blinded. Outcomes 8pm to 7am, monitored by nurse
Incomplete outcome data (attrition bias) All outcomes	High risk	Insufficient outcome assessed. Loss of 8/17 patients
Selective reporting (reporting bias)	High risk	Primary outcomes not assessed in sufficient detail
Other bias	High risk	Insufficient information

Lucchesi 1949

Methods	Quasi-random allocation (alternation). Blinding and intention-to-treat analysis was not reported. Loss to follow-up was unclear
Participants	Both male and female inpatients under the age of 1 year. Vaccination status and previous antibiotic treatment were not reported. Clinical and bacteriologically diagnosed pertussis
Interventions	Pertussis immune serum, 50 to 100 ml intravenously on admission followed by 50 ml/day until improvement, or 5 doses

Lucchesi 1949 (*Continued*)

Outcomes	Frequency of paroxysms of cough	
Notes	-	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Alternate allocation
Allocation concealment (selection bias)	High risk	Patients divided into 2 groups; each group included the alternate patients admitted without selection
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding of participants, personnel or assessor
Incomplete outcome data (attrition bias) All outcomes	High risk	-
Selective reporting (reporting bias)	High risk	Inadequate details in protocol
Other bias	High risk	Different doses given. Numerous potential confounders

Mertsola 1986

Methods	Method of randomisation was not stated. Was a double-blinded study. Intention-to-treat analysis was not reported. Loss to follow-up was unclear	
Participants	Outpatients, all vaccinated (gender not specified) with a mean age of 9.4 years in the treatment group and 7.5 years in the control group. 14.8% received previous antibiotic treatment and all the participants had been previously vaccinated. Bacteriologically and serologically confirmed pertussis	
Interventions	Salbutamol orally 0.1 mg/kg orally 3 times a day for 10 days	
Outcomes	Number of paroxysms of cough	
Notes	-	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Mertsola 1986 (*Continued*)

Random sequence generation (selection bias)	High risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Double-blinded but no details provided. Randomised controls received a corresponding dose of placebo
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Insufficient details. Unclear if personnel were blinded or assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	-
Selective reporting (reporting bias)	Unclear risk	Not clear if intention-to-treat
Other bias	High risk	Method of assessing outcomes not stated

Miraglia 1984

Methods	Method of randomisation was unclear. A double-blind, placebo-controlled, trial. Intention-to-treat analysis was not reported. 100% follow up
Participants	Both male and female patients, age range 12 months to 11 years in the treatment group and 10 months to 12 years in the control group. Vaccination status and previous antibiotic treatment were not reported. Clinically diagnosed pertussis
Interventions	Chlophedianol 1.62 mg/kg/day orally plus sobrerol 3.6 mg/kg/day orally
Outcomes	Severity of paroxysms of cough
Notes	Placebo was a syrup base

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of randomisation was not stated
Allocation concealment (selection bias)	Unclear risk	Double-blinded but no details provided
Blinding (performance bias and detection bias) All outcomes	High risk	No indication if blinding was effective. Placebo base was a syrup (sciroppo)

Miraglia 1984 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Sufficient details were provided to address this
Selective reporting (reporting bias)	Low risk	-
Other bias	Unclear risk	Evaluation of symptoms was subjective and based on a score sheet for staff and parents to use

Pavesio 1977

Methods	Method of randomisation was not stated. Placebo-controlled trial. Intention-to-treat analysis was not reported. Follow-up unclear
Participants	Inpatients (gender not specified), age range 6 months to 3 years, coughing for less than 21 days. None had been previously vaccinated. Previous antibiotic treatment was not reported. Clinically diagnosed pertussis
Interventions	Salbutamol 0.5 mg/kg/day orally in 3 doses for 15 days
Outcomes	Frequency of paroxysms of cough, frequency of whoops
Notes	Erythromycin oral 40 mg/kg/day for 10 days. Placebo saccharin

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Appears to have used 'random' allocation in unspecified way
Allocation concealment (selection bias)	High risk	Insufficient details reported
Blinding (performance bias and detection bias) All outcomes	High risk	Placebo syrup was saccharin. Unclear if participants, personnel or assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Data not reported in a way to assess this
Selective reporting (reporting bias)	High risk	Data not reported in a way to assess this
Other bias	High risk	Unclear how outcomes were measured

Roberts 1992

Methods	Method of randomisation was not stated (hospital pharmacy was responsible for assignment of patients to treatment groups). Was a double-blind, placebo-controlled trial. Intention-to-treat analysis was not reported. 100% follow-up
Participants	Inpatients (gender not specified) less than 6 months of age. Vaccination status and previous antibiotic treatment were not reported. Clinically diagnosed pertussis
Interventions	Dexamethasone 0.3 mg/kg/day for 4 days. Route of administration not stated
Outcomes	Percentage reduction in paroxysms of cough between baseline and post-treatment period (48 hours), duration of hospital stay
Notes	Erythromycin 40 mg/kg/day for 14 days

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not stated. 7 patients in intervention, 4 in control
Allocation concealment (selection bias)	Unclear risk	Central randomisation by hospital pharmacy
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Used placebo but no details provided. Not stated if participant, personnel or assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Insufficient details provided
Selective reporting (reporting bias)	Unclear risk	Details of paroxysms absolute number not given, only % reduction
Other bias	Unclear risk	Unclear how outcomes measured

Zoumboulakis 1973

Methods	Quasi-random allocation (alternation). Stated that an observer was blinded. Intention-to-treat analysis was not reported. 94.5% follow up. No placebo stated
Participants	Both male and female inpatients coughing for less than 3 weeks. Age range of 15 days to 3 years. 92.7% were not previously vaccinated and 7.3% had incomplete vaccination. None had previous antibiotic treatment. Clinically diagnosed pertussis
Interventions	Hydrocortisone 30 mg/kg/day intramuscularly for 2 days followed by a reduced dosage over 6 days

Zoumboulakis 1973 (*Continued*)

Outcomes	Mean number of paroxysms of cough, mean number of whoops, mean number of vomits
Notes	Erythromycin given orally 40 mg/kg/day for 10 days. Coughing episodes assessed and scored by blinded nurse

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Alternate allocation
Allocation concealment (selection bias)	High risk	Baseline characteristics differ between groups
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding of participants, assessors apparently blinded, unclear if personnel were blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient details reported to assess this
Selective reporting (reporting bias)	Low risk	-
Other bias	High risk	Unclear how outcomes were measured

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

Study	Reason for exclusion
Ames 1953	Sampling was reported as 'using the lottery method' (implying chance allocation to treatment groups). Gross baseline imbalances between groups appeared unlikely to be due to random allocation and in any event a fatal flaw in validity
Badr-El-Din 1976	Patients were randomly allocated to 1) chloramphenicol, 2) chloramphenicol and prednisone or 3) chloramphenicol and salbutamol. Large baseline differences were reported between the chloramphenicol only group and the other 2 treatment groups. No explanation was given for having 2 chloramphenicol groups
Balagtas 1971	Random allocation was abandoned during an epidemic when all patients were immunised. Data for randomly allocated patients before the epidemic were not reported
Bertaggia 1972	Random allocation unclear, no allocation concealment stated or blinding of participants or personnel. Study performed over an 8-year period

(*Continued*)

Brunskill 1986	Allocation method unclear, no direct comparison of treatment and control. Graphical representation of the allocation sequence in the results was not consistent with allocation sequence described in the text
Bruss 1999	Comparison of 2 doses of pertussis immunoglobulin without comparison with placebo or no treatment
Chandra 1972	Method of allocation not stated
Eichlseder 1963	Patients assigned in an alternating manner to either (chloramphenicol succinate) or (chloramphenicol and pertussis-immunoglobulin) or (pertussis-immunoglobulin and oxytetracycline). The only control group was for chloramphenicol succinate. Alternating system to allocate patients stated to be age to intervention
Giuliani 1966	Random allocation unclear, no allocation concealment stated or blinding of participants or personnel. Methods unclear. Study performed over a 10-year period
Leen 1989	Randomisation performed by random code. No placebo. Another intervention stated to be used for children with complications but no details provided or number of children with extra intervention
Lewis 1984	No head-to-head comparison was made between the group receiving Drosera and the group receiving Sac Lac. Positive or negative response to treatment was determined subjectively by parents. Effectively a before-after study with the patients in "treatment group A" that received Sac Lac compared with the non-responders in 'treatment group B'
Musso 1982	No allocation sequence generated, no allocation concealment or blinding stated. Control and intervention group received antibiotic and pertussis immunoglobulin treatment prior to other intervention
Pavesio 1979	Controlled trial with no random allocation and no mention of methods
Sacchetti 1982	Allocation method unclear, no direct comparison of treatment and control
Torre 1993	No allocation sequence generated, no allocation concealment or blinding stated. No controls stated

DATA AND ANALYSES

Comparison 1. Antihistamines versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Paroxysms of cough (per 24 hours)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only

Comparison 2. Pertussis immunoglobulin versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duration of hospital stay (days)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
2 Mean number of whoops per 24 hours (first week)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
3 Mean whoops per hour	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
4 Mean paroxysmal cough per hour	1		Mean Difference (IV, Random, 95% CI)	Subtotals only

Comparison 3. Steroids versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Duration of hospital stay (days)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only

Comparison 4. Salbutamol versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Paroxysms of cough (per 24 hours)	2	42	Mean Difference (IV, Fixed, 95% CI)	-0.22 [-4.13, 3.69]

Analysis 1.1. Comparison 1 Antihistamines versus placebo, Outcome 1 Paroxysms of cough (per 24 hours).

Review: Symptomatic treatment of the cough in whooping cough

Comparison: 1 Antihistamines versus placebo

Outcome: 1 Paroxysms of cough (per 24 hours)

Study or subgroup	Diphenhydramine N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Danzon 1988	25	22.6 (13.1)	24	20.7 (10.2)			1.90 [-4.66, 8.46]
Subtotal (95% CI)	**0**		**0**				**0.0 [0.0, 0.0]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.0 (P < 0.00001)

Analysis 2.1. Comparison 2 Pertussis immunoglobulin versus placebo, Outcome 1 Duration of hospital stay (days).

Review: Symptomatic treatment of the cough in whooping cough

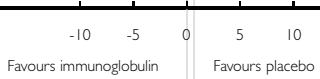
Comparison: 2 Pertussis immunoglobulin versus placebo

Outcome: 1 Duration of hospital stay (days)

Study or subgroup	[Not identical] N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Granstrom 1991	32	5 (3.2)	14	5.7 (5.5)			-0.70 [-3.79, 2.39]
Subtotal (95% CI)	**0**		**0**				**0.0 [0.0, 0.0]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.0 (P < 0.00001)



Analysis 2.2. Comparison 2 Pertussis immunoglobulin versus placebo, Outcome 2 Mean number of whoops per 24 hours (first week).

Review: Symptomatic treatment of the cough in whooping cough

Comparison: 2 Pertussis immunoglobulin versus placebo

Outcome: 2 Mean number of whoops per 24 hours (first week)

Study or subgroup	[Not identical] N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Granstrom 1991	33	1.7 (3.1)	14	4.8 (5.6)			-3.10 [-6.22, 0.02]
Subtotal (95% CI)	**0**		**0**				**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.0 (P < 0.00001)							

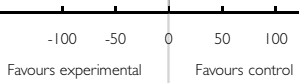
Analysis 2.3. Comparison 2 Pertussis immunoglobulin versus placebo, Outcome 3 Mean whoops per hour.

Review: Symptomatic treatment of the cough in whooping cough

Comparison: 2 Pertussis immunoglobulin versus placebo

Outcome: 3 Mean whoops per hour

Study or subgroup	[Not identical] N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Halperin 2007	17	0.394 (0.375)	7	0.46 (0.284)			-0.06 [-0.34, 0.21]
Subtotal (95% CI)	**0**		**0**				**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.0 (P < 0.00001)							



Analysis 2.4. Comparison 2 Pertussis immunoglobulin versus placebo, Outcome 4 Mean paroxysmal cough per hour.

Review: Symptomatic treatment of the cough in whooping cough

Comparison: 2 Pertussis immunoglobulin versus placebo

Outcome: 4 Mean paroxysmal cough per hour

Study or subgroup	[Not identical] N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Halperin 2007	17	0.732 (0.463)	7	0.81 (0.355)			-0.07 [-0.42, 0.27]
Subtotal (95% CI)	**0**		**0**				**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.0 (P < 0.00001)							

Analysis 3.1. Comparison 3 Steroids versus placebo, Outcome 1 Duration of hospital stay (days).

Review: Symptomatic treatment of the cough in whooping cough

Comparison: 3 Steroids versus placebo

Outcome: 1 Duration of hospital stay (days)

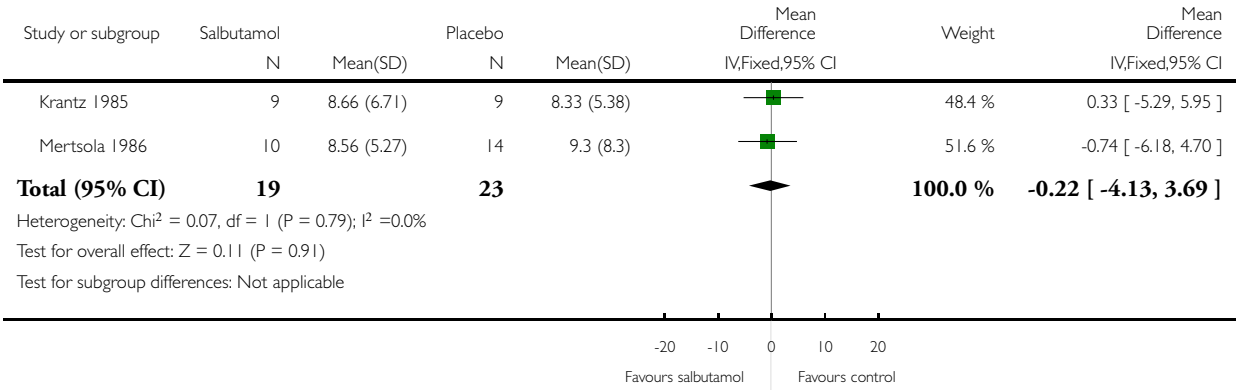
Study or subgroup	Dexamethasone N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Roberts 1992	7	14.3 (8.67)	4	17.75 (10.21)			-3.45 [-15.34, 8.44]
Subtotal (95% CI)	**0**		**0**				**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.0 (P < 0.00001)							

Analysis 4.1. Comparison 4 Salbutamol versus placebo, Outcome 1 Paroxysms of cough (per 24 hours).

Review: Symptomatic treatment of the cough in whooping cough

Comparison: 4 Salbutamol versus placebo

Outcome: 1 Paroxysms of cough (per 24 hours)



ADDITIONAL TABLES

Table 1. Results for pre-specified outcomes reported in included studies

Study ID	Intervention	Outcomes	Results
Lucchesi 1949	Pertussis immune serum 50 to 100 ml on admission followed by 50 ml daily until improvement or 5 doses	Frequency of paroxysms of cough	Results were presented graphically as means of means of 7-day periods - unable to extract data from the graphs provided As described by previous authors (Pillay 2003) the conclusion (from visual inspection of graphs) - "The patients who received serum showed a more regular decline in the rate of frequency of paroxysms when treated in the first week of disease than did the patients in the control group" Side effects were not reported
Pavesio 1977	Salbutamol 0.5 mg/kg/day in 3 doses for 15 days	Frequency of paroxysms of cough, frequency of whoops	Data presented graphically Extracted from graphs N = 50 Mean number of episodes of cough per 24 hours (day 2 only)

Table 1. Results for pre-specified outcomes reported in included studies (*Continued*)

			Salbutamol - 8.5 Placebo - 12.3 Mean number of episodes of whoop per 24 hours (day 2 only) Salbutamol - 2.0 Placebo - 6.1 Side effects were not reported
Miraglia 1984	Chlophedianol 1.62 mg/kg/day plus sobrerol 3.6 mg/kg/day	Severity of paroxysms of cough	Semi-quantitative score of severity of paroxysms - scale of 0 to 4 N = 15 Chlophedianol and sobrerol - 0.80 Placebo - 1.3 Side effect reported was diarrhoea in 6.7% of the placebo group. Authors stated that the diarrhoea was not related to being a part of the study as event of diarrhoea was recorded 2 days after treatment with placebo
Zoumboulakis 1973	Hydrocortisone 30 mg/kg/day for 2 days followed by a reduced dosage over 6 days	Number of paroxysms of cough, number of whoops, number of vomits	Data presented graphically N = 145 Mean number of episodes of cough per 24 hours (day 2 only) Hydrocortisone - 16 No treatment - 17.9 Mean number of episodes of whoop per 24 hours (day 2 only) Hydrocortisone - 7 No treatment - 7.8 Mean number of episodes of vomiting per 24 hours (day 2 only) Hydrocortisone - 4 No treatment - 4 Side effects reported were pulmonary infiltrates in 15.1% of the hydrocortisone group and 10.7% of the control group

APPENDICES

Appendix 1. EMBASE search strategy

1. (whoop* or pertus*).tw.
2. Pertussis/
3. Bordetella pertussis/
4. 1 or 3 or 2
5. exp Vaccine/
6. exp Antibiotic Agent/
7. 5 or 6
8. 4 not 7
9. Salbutamol/ or Ipratropium Bromide/
10. (salbutamol or albuterol or ventmax or ventolin or volmax or airomir or asmasal or salamol or salbulin).tw.
11. beta agonist*.tw.
12. Beta Adrenergic Receptor Stimulating Agent/
13. (inhaler* or nebuliser* or nebulizer* or bronchodilator* or vaporiser* or vaporizer*).tw.
14. exp inhaler/ or nebulizer/
15. Bronchodilating Agent/ or Bronchodilation/
16. (steroid* or corticosteroid* or corticoid* or glucocorticoid* or cortison* or prednisone or prednisolone or hydrocortisone).tw.
17. exp Steroid/
18. (mucolytic* or carbocisteine or erdosteine or erdotin or mecysteine or methyl cysteine or visclair or mucoactive).tw.
19. exp Mucolytic Agent/ or exp Antitussive Agent/
20. (cough adj5 suppress*).tw.
21. (antitussive or anti tussive or protussive or pro tussive).tw.
22. codeine.tw.
23. (cough adj5 (remed* or therap* or treatment* or management or medicine* or medication*)).tw.
24. (pholocodine or dextromethorphan or linctus).tw.
25. (demulcent* or ipecacauanha or expectorant*).tw.
26. (decongestant* or ephedrine or oxymetazoline or phenylephrine or pseudoephrine or xylometazoline).tw.
27. (sudafed or galpseud or galenphol or benylin or calpol or tixulix or robitussin or galsud or actifed or vicks).tw.
28. (sedative* or diazepam or phenobarbitone or phenobarbital or chlorpromazine or largactil).tw.
29. (benadryl or diphenhydramide or promethazine or brompheniramine or chlorphenamine or doxylamine or triprolidine or chlorphenizamine or phenergan or piriton or anti histamine* or antihistamin* or histamine antagonist*).tw.
30. (sedat* or diazepam or phenobarbitone or phenobarbitol or chlorpromazine or largactil).tw.
31. exp Hypnotic Sedative Agent/
32. exp Antihistaminic Agent/
33. (honey or glycerol or zinc or glycerin).tw.
34. Honey/
35. exp Glycerol/
36. (anticholinergic adj (drug or agent* or therap*)).tw.
37. cholinergic antagonist*.tw.
38. exp Cholinergic Receptor Blocking Agent/
39. Levdropropizine/
40. levodropropizine.tw.
41. Moguisteine/
42. moguisteine.tw.
43. ipratropium bromide.tw.
44. or/9-43
45. 4 and 44
46. 8 or 45
47. limit 46 to "treatment (2 or more terms high sensitivity)"

Appendix 2. CINAHL search strategy

Search ID #	Search Terms
S44	S8 or S42 (**Limiters** - Clinical Queries: Therapy - High Sensitivity)
S43	S8 or S42
S42	S4 and S41
S41	S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33 or S34 or S35 or S36 or S37 or S38 or S39 or S40
S40	TI levodropropizine or AB levodropropizine or TI ipratropium bromide or AB ipratropium bromide or TI moguisteine or AB moguisteine
S39	(MH "Cholinergic Antagonists+")
S38	TI cholinergic antagonist* or AB cholinergic antagonist*
S37	TI (anticholinergic drug or anticholinergic agent* or anticholinergic therap*) or AB (anticholinergic drug or anticholinergic agent* or anticholinergic therap*)
S36	TI (sedat* or diazepam or phenobarbitone or phenobarbitol or chlorpromazine or largactil) or AB (sedat* or diazepam or phenobarbitone or phenobarbitol or chlorpromazine or largactil)
S35	(MH "Hypnotics and Sedatives+")
S34	TI (honey or glycerol or zinc or glycerin) or AB (honey or glycerol or zinc or glycerin)
S33	(MH "Zinc") or (MH "Zinc Compounds+")
S32	(MH "Glycerin+")
S31	(MH "Honey")
S30	TI (benadryl or diphenhydramide or promethazine or brompheniramine or chlorphenamine or doxylamine or triprolidine or chlorphenizamine or phenergan or piriton or anti histamine* or antihistamin* or histamine antagonist*) or AB (benadryl or diphenhydramide or promethazine or brompheniramine or chlorphenamine or doxylamine or triprolidine or chlorphenizamine or phenergan or piriton or anti histamine* or antihistamin* or histamine antagonist*)
S29	(MH "Histamine Antagonists+")
S28	TI cough N5 remed* or AB cough N5 therap* or TI cough N5 therap* or AB cough N5 treatment* or TI cough N5 treatment* or AB cough N5 medicine* or TI cough N5 medicine* or AB cough N5 medication* or TI cough N5 medication* or AB cough N5 remed*

(*Continued*)

S27	TI (sudafed or galpseud or galenphol or benylin or calpol or tixulix or robitussin or galsud or actifed or vicks) or AB (sudafed or galpseud or galenphol or benylin or calpol or tixulix or robitussin or galsud or actifed or vicks)
S26	TI (decongestant* or ephedrine or oxymetazoline or phenylephrine or pseudoephrine or xylometazoline) or AB (decongestant* or ephedrine or oxymetazoline or phenylephrine or pseudoephrine or xylometazoline)
S25	TI (demulcent* or ipecacauanha or expectorant*) or AB (demulcent* or ipecacauanha or expectorant*)
S24	TI (pholocodine or dextromethorphan or linctus) or AB (pholocodine or dextromethorphan or linctus)
S23	TI codeine or AB codeine
S22	TI (antitussive or anti tussive or protussive or pro tussive) or AB (antitussive or anti tussive or protussive or pro tussive)
S21	(MH "Antitussive Agents+")
S20	TI cough N5 suppress* or AB cough N5 suppress*
S19	TI (mucolytic* or carbocisteine or erdosteine or erdotin or mecysteine or methyl cysteine or visclair or mucoactive) or AB (mucolytic* or carbocisteine or erdosteine or erdotin or mecysteine or methyl cysteine or visclair or mucoactive)
S18	(MH "Expectorants+")
S17	TI (steroid* or corticosteroid* or corticoid* or glucocorticoid* or cortison* or prednisone or prednisolone or hydrocortisone) or AB (steroid* or corticosteroid* or corticoid* or glucocorticoid* or cortison* or prednisone or prednisolone or hydrocortisone)
S16	(MH "Adrenal Cortex Hormones+")
S15	(MH "Steroids")
S14	(MH "Nebulizers and Vaporizers")
S13	TI (inhaler* or nebuliser* or nebulizer* or bronchodilator* or vaporiser* or vaporizer*) or AB (inhaler* or nebuliser* or nebulizer* or bronchodilator* or vaporiser* or vaporizer*)
S12	TI beta agonist* or AB beta agonist*
S11	(MH "Adrenergic Beta-Agonists")
S10	(MH "Albuterol")
S9	TI (salbutamol or albuterol or ventmax or ventolin or volmax or airomir or asmasal or salamol or salbulin) or AB (salbutamol or albuterol or ventmax or ventolin or volmax or airomir or asmasal or salamol or salbulin)
S8	S4 not S7

(*Continued*)

S7	S5 or S6
S6	(MH "Antibiotics+")
S5	(MH "Vaccines+")
S4	S1 or S2 or S3
S3	TI (whoop* or pertus*) or AB (whoop* or pertus*)
S2	(MH "Bordetella Pertussis")
S1	(MH "Whooping Cough")

Appendix 3. AMED search strategy

whoop* or pertus*

Appendix 4. LILACS search strategy

1. whoop$ or pertus$
2. estud$ or clin$ or grupo$
3. 1 and 2

Appendix 5. Search strategy, *Pillay 2003*

MEDLINE was searched using the following search strategy. Search date: June 2003
1 exp WHOOPING COUGH/
2 exp BORDETELLA PERTUSSIS/
3 whooping.mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading]
4 pertussis.mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading]
5 or/1-4
6 exp VACCINES/
7 exp ANTIBIOTICS/
8 or/6-7
9 5 not 8
10 RANDOMIZED CONTROLLED TRIAL.pt.
11 CONTROLLED CLINICAL TRIAL.pt.
12 RANDOMIZED CONTROLLED TRIALS.sh.
13 RANDOM ALLOCATION.sh.
14 DOUBLE BLIND METHOD.sh.
15 SINGLE-BLIND METHOD.sh.
16 or/10-15
17 (ANIMAL not HUMAN).sh.
18 16 not 17
19 CLINICAL TRIAL.pt.
20 exp Clinical Trials/
21 (clin$ adj25 trial$).ti,ab.

22 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
23 PLACEBOS.sh.
24 placebo$.ti,ab.
25 random$.ti,ab.
26 or/19-25
27 26 not 17
28 18 or 27
29 9 and 28
Additional information was identified in EMBASE using a similar search strategy. Search date: June 2003
LILACS was searched using the following search terms:
Whooping Cough OR Pertussis OR Bordetella OR Respiratory
Search date: November 2001

WHAT'S NEW

Last assessed as up-to-date: 12 January 2012.

Date	Event	Description
12 January 2012	New search has been performed	Searches updated. No new studies identified as being suitable for inclusion in this review
12 January 2012	New citation required but conclusions have not changed	Kay Wang joined the authors to update this review.

HISTORY

Protocol first published: Issue 4, 2001

Review first published: Issue 4, 2003

Date	Event	Description
9 April 2009	New citation required but conclusions have not changed	A new team of review authors took over and updated this review in 2009
9 April 2009	New search has been performed	Searches conducted. We included one trial since the review was first published in 2003
7 July 2008	Amended	Withdrawn Issue 4, 2004.
11 April 2008	Amended	Converted to new review format.
9 June 2003	New search has been performed	Searches conducted.

CONTRIBUTIONS OF AUTHORS

Silvana Bettiol (SB), Matthew Thompson (MT) and Nia Roberts (NR) participated in study selection, data extraction and analysis.

Kay Wang (KW) assisted in screening new articles identified in the updated searches in 2012.

SB, KW, MT, NR, Rafael Perera (RP), Carl Heneghan (CH) and Anthony Harnden (AH) contributed to the writing of the updated review in 2012.

DECLARATIONS OF INTEREST

None declared.

SOURCES OF SUPPORT

Internal sources

- The Department of Primary Health Care is part of HIHR School of Primary Care Research, UK.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Albuterol [therapeutic use]; Anti-Inflammatory Agents [therapeutic use]; Cough [*drug therapy; etiology]; Dexamethasone [therapeutic use]; Diphenhydramine [therapeutic use]; Histamine H1 Antagonists [therapeutic use]; Immunoglobulins [therapeutic use]; Randomized Controlled Trials as Topic; Whooping Cough [complications; *drug therapy]

MeSH check words

Adult; Child; Humans