A SYSTEMATIC REVIEW OF THE
SYMPTOMATIC TREATMENT OF THE
COUGH IN WHOOPING COUGH

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Dissertation submitted in partial fulfilment of the requirements of the
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Department of Public Health

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DECLARATION

I, Victoria Pillay hereby declare that the work on which this thesis is based is my original work (except where acknowledgements indicate otherwise), and that neither the whole work nor any part has been, or is to be submitted for another degree in this or any other university.

________________________________
Signature

________________________________
Date
Dedicated to my fiancé Brian Van Wyk and friends, Amy Tertiens and Tess Rodrigues who are all pursuing higher degrees. Always remember the sky is the limit and you can achieve anything you set your mind to. So dream big...
ACKNOWLEDGEMENTS

I praise GOD for the inspiration to start, courage to continue and strength to finish this dissertation.

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Contribution of Author

The topic for the review was provided by my supervisor, Prof. George Swingler. I was the principal investigator on the project. I developed the protocol, data extraction form and composed the letters sent out to authors. I coordinated the project, interacted with the various Cochrane Centres, the Acute Respiratory Infections Group, translators and the pharmaceutical companies. I also did the data analysis, interpreted the findings and wrote the report. The nature of the review process required that study selection and data extraction to be done in duplicate - Prof. Swingler was the second reviewer.
ABSTRACT

Background: There are between 20 - 40 million cases of whooping cough annually world-wide, 90% of which occur in developing countries, resulting in an estimated 200 - 300 000 fatalities each year. Much of the morbidity is due to the paroxysmal cough. Corticosteroids, salbutamol (a $\beta_2$ - adrenergic stimulant), and pertussis-specific immunoglobulin have been proposed as standard treatment for the cough. Antihistamines have also been administered. No systematic review of the effectiveness of any of these interventions or others has been performed.

Objective: In this systematic review we aim to assess the effectiveness of interventions used to reduce the severity of the coughing paroxysms in whooping cough in children and adults.

Selection criteria: Randomised and quasi randomised controlled trials of any intervention that reduced the severity of the coughing paroxysms in whooping cough; excluding antibiotics and vaccines.

Study selection: All interventions aimed at reducing the severity of the coughing paroxysms in children or adults with whooping cough with any of the following outcome measures met inclusion criteria for the review; i) frequency of paroxysms of coughing (primary outcome), ii) frequency of vomiting, iii) frequency of whoop, iv) frequency of cyanotic spells, v) development of serious complications, vi) mortality from any cause, vii) side effects due to medication, viii) admission to hospital, and ix) duration of hospital stay.

Search strategy: We searched the Cochrane Controlled Trials register, Acute Respiratory Infectious Disease Group Specialised Trials register, MEDLINE,
LILACS, scanned reference lists of identified trials, contacted authors of identified trials and the relevant pharmaceutical companies.

**Data collection and analysis:** Studies were selected, quality assessed and data extracted by two reviewers independently.

**Results:** Nine studies satisfied the inclusion criteria but four had insufficient data for further meta-analysis of our pre-specified outcomes. Studies were old and poorly reported. The largest study had a total sample size of 49 and the smallest study nine. All studies were performed in industrialised settings.

Eligible studies assessed diphenhyramine, pertussis immunoglobulin, dexamethasone and salbutamol. No statistically significant benefit was found for any of the interventions. Diphenhyramine was associated with a mean increase of 1.90 coughing spells per 24 hours [95%CI – 4.66; 8.46] and pertussis immunoglobulin a mean decrease in hospital stay of 0.70 days [95% CI -3.79; 2.39], and a mean reduction of 3.10 whoops per 24 hours [95% CI – 6.22; 0.02]. Dexamethasone resulted in a mean decrease in hospital stay of 3.45 days [95% CI – 15.34; 8.44] and salbutamol in a weighted mean decrease in coughing paroxysms of 0.95 per 24 hours [95% CI – 6.21; 4.31].

**Reviewers’ conclusion:** Although assessments have been performed on a whole range of interventions, including diphenhyramine, pertussis immunoglobulin, dexamethasone and salbutamol, insufficient evidence exists to draw conclusions about the effects of any of them.
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1. INTRODUCTION

1.1 Whooping Cough

Whooping cough (pertussis) is a communicable, respiratory disease transmitted by coughing and sneezing (Johnston 2000) and caused by the bacterium Bordetella pertussis. This disease is most severe in children, particularly those under the age of 12 months (Johnston 2000). Adults suffer from milder forms of the disease and the cough is usually less severe (AAP 1997).

Although several organisms may cause a disease similar to whooping cough, severe cases are due to Bordetella pertussis (Hallander 1999). Disease from B. pertussis can be prevented by vaccination. However, despite widespread immunization with pertussis vaccine, there are still between 20 - 40 million cases of pertussis annually world-wide, 90% of which occur in developing countries, resulting in an estimated 200 - 300 000 fatalities each year (WHO 1999).

The first symptoms of whooping cough are similar to those of a "common cold," which are a runny nose, dry cough and mild fever. After about one to two weeks, coughing begins to occur in spells (paroxysms) that may last for over a minute. Between paroxysms, the child may gasp for air with a characteristic "whooping" sound - although infants may not "whoop" as older children do. The cough usually lasts at least two weeks before gradually improving but may persist for more than three months (Feigin 1992). Severe coughing paroxysms cause vomiting which may lead to malnutrition and dehydration, an especially
perilous problem for infants in developing countries (Long 2000). Other severe but less common consequences of the cough include cerebral hypoxia, subcutaneous emphysema or pneumothorax (presence of air in the subcutaneous tissue or pleural space) and cerebral haemorrhage (Feigin 1992). Nevertheless, even without severe complications the coughing spasms are very distressing for both the child and parents.

Treatment options depend on the stage of disease. Prevention of the infection by immunisation against Bordetella pertussis is effective, but not fully so since some whole cell vaccines displayed a level of toxicity which discourages immunisation (Tinnion 2000). Furthermore immunisation does not confer life long immunity or protect against other similar organisms. Antibiotic treatment during the early stage that resembles the common cold is said to shorten the course of the illness. The difficulty with this treatment, however, is that there is no reason to give an antibiotic for what appears to be just a common cold. Administering antibiotics at a later stage, once the cough has developed and a clear diagnoses is made, is said not to change the character of the cough although treatment does render the patient non infectious (Johnston 2000). Therefore treatment of the cough is symptomatic, i.e. treatment aims to reduce the severity of the coughing paroxysms until the disease has run its course (Long 2000).

Several interventions have been considered to reduce the severity of the coughing paroxysms. Corticosteroids, salbutamol (a β₂ - adrenergic stimulant), and pertussis-specific immunoglobulin have been proposed as standard treatment for the cough (AAP 1997). Antihistamines have also been
administered. Conflicting views have been expressed about the effectiveness and usefulness of these interventions (Hewlett 2000, Bass 1985) but no systematic review has been done to assess their effects.

As it is currently difficult to diagnose whooping cough early enough to treat the disease with antibiotics, the next best option is treatment focused on reducing the severity of the coughing paroxysms until the disease runs its course. In this systematic review we aim to assess the effectiveness of all interventions used to reduce the severity of the coughing paroxysms in whooping cough in children and adults.

1.2 Literature Reviews

1.2.1 Unsystematic literature reviews

Medical literature reviews should provide a readable summary of all the evidence in a manner that is unbiased, transparent and up to date. Narrative, unsystematic medical reviews do not routinely use scientific methods to identify, assess, and synthesise information (Mulrow 1987). Often reviewers fail to report on the literature searches used to identify studies (Joyce 1998). These reviews are subject to many biases due to incomplete literature searches, bias in study selection and inadequate attention to trial quality. Incomplete literature searches include "file drawer bias" where only literature that the reviewer and colleagues have been collecting are considered. Furthermore, publication bias can occur, where trials with statistically significant findings are more likely to be published (Easterbrook 1991) or language bias where statistically significant results are more likely to be published in English (Egger 1997). Incomplete literature searches can lead to an overestimate of effects in both instances.
Bias in study selection has been demonstrated in a study of reviews of chronic fatigue syndrome where citations were heavily influenced by the authors' discipline or nationality (Joyce 1998).

Empirical evidence is also available on biases associated with the absence of the study design features allocation concealment, blinding and intention to treat analysis in randomised controlled trials (Schultz 1995). In general poorer quality studies overestimate the effects of interventions.

1.2.2 Systematic literature reviews

Systematic literature reviews differ from traditional narrative literature reviews in that they are in themselves research projects, with a pre specified protocol which consists of an exhaustive literature search strategy, explicit criteria for studies to be included in the review and the application of methodological rigour for extraction and analysis of data. The use of explicit, systematic methods in reviews limits bias (systematic errors), thus providing more reliable results upon which to draw conclusions and make decisions. The use of statistical methods to synthesise the results of independent studies (meta analysis), can provide more precise estimates of the effects of healthcare interventions than those derived from the individual studies included in a review (Cochrane Reviewers Handbook, 2001).

1.2.3 The Cochrane Collaboration and systematic reviews.

The Cochrane Collaboration is an international organisation that aims to help people make well-informed decisions about healthcare by preparing, maintaining and promoting the accessibility of systematic reviews of the effects
of healthcare interventions (Cochrane Collaboration 2002). Cochrane systematic reviews are prepared following a standard internationally recognized procedure of the Cochrane Collaboration (Cochrane Reviewers Handbook, 2001). This review has been prepared under the auspices of the International Editorial Board of the Cochrane Acute Respiratory Infections Group.
2. METHODS

2.1 Objective

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

2.2 Inclusion criteria for studies for this review

2.2.1 Types of studies

Randomised controlled trials and quasi-randomised trials comparing the effects of interventions aimed at reducing the severity of the coughing paroxysms with either:

a) Another treatment for the cough (if at least one [at the same dosage] has also been compared to placebo or no treatment in the same or another trial)

b) Placebo

c) No treatment

2.2.2 Types of participants

Children or adults with whooping cough (as diagnosed by the trial authors), either in hospital or at home.

2.2.3 Types of interventions

Interventions aimed at reducing the severity of the coughing paroxysms in whooping cough including bronchodilators (oral and inhaled), steroids (oral and inhaled), antihistamines and pertussis immunoglobulin (infusion).
2.2.4 Types of outcome measures

Severity of the cough determined by any of the following:

a) Frequency of paroxysms of coughing (primary outcome measure)
b) Frequency of vomiting
c) Frequency of whoop
d) Frequency of cyanosis (turning blue) during cough
e) Development of a serious complication e.g. cerebral haemorrhage or convulsions or presence of subcutaneous emphysema or pneumothorax
f) Mortality from any cause
g) Side effects of medication (as defined by authors of identified trials)
h) Admission to hospital
i) Duration of hospital stay (if admitted before randomisation)

2.3 Excluded

Interventions aimed at preventing the onset of cough e.g. vaccines. Antibiotics were also excluded since the effectiveness of antibiotics will require a systematic review of its own as the issues of timing of antibiotic administration would need a different approach.

2.4 Search strategy for identification of studies

a) In an attempt to identify all existing randomised controlled trials in any language, the following databases were searched (see Appendix 1 for all search strategies):

(i) The Cochrane Controlled Trials Register – This is the most comprehensive data base of randomised controlled trials, containing reports of randomised controlled trials and possible randomised

(ii) The Cochrane Acute Respiratory Infections Group trials register (search strategy as composed and done by the Acute Respiratory Infections Group). This database consists of additional trials identified by the Group (i.e. through current hand searching of 52 journals) that have not yet been submitted to the Cochrane Controlled Trials Register.

(iii) MEDLINE (1966 onwards).

(iv) LILACS - This data base indexes 670 health science journals from the Latin American and Caribbean region. Only 41 of these health science journals are indexed in MEDLINE/EMBASE (Otavio 2001). Latin American and Caribbean health science production is almost absent from international data bases hence the need to search this data base for possible trials (Regina 2000). (Search strategy as composed by the Brazilian Cochrane Centre together with the Acute Respiratory Infections Group and done in Australia).

b) We also scanned reference lists of identified articles for further potentially eligible trials.

c) We contacted authors of the identified trials.

d) We contacted pharmaceutical companies producing the interventions studied in identified trials for additional published and unpublished trials or other studies meeting our inclusion criteria.
2.5 Selection of trials

Two investigators (author and supervisor) independently screened the results of the literature search and selected eligible studies according to the preset criteria. Differences were resolved by discussion.

2.6 Data extraction

Data extraction was performed by both investigators independently using a pre piloted data extraction form (Appendix 2). Differences between investigators were resolved by discussion.

For potentially eligible foreign language articles, help was requested from Cochrane Centres in the relevant countries or from colleagues who understood the language. Translators first provided a brief summary of articles, including information on inclusion criteria. Both investigators independently reviewed these summaries and selected eligible studies. Discussion and contacting translators for additional information resolved differences when they occurred. For eligible studies data extraction forms, a protocol and the list of selected studies were then forwarded to the translators who did data extraction.

The following clinical information was extracted from each trial (in whatever language): participants (age and gender); criteria used to diagnose whooping cough; interventions and outcomes including side effects. Aspects of trial quality and reporting that were recorded were adequacy of allocation concealment, blinding, loss to follow up and use of an intention to treat analysis. These quality markers were reported individually and not as a score.
2.6.1 Definitions for markers of trial quality and reporting

a) Randomisation

Random allocation was accepted if it was stated as being performed and no collateral evidence indicated otherwise.

b) Quasi-randomization

(i) Allocation of participants to different treatment groups was not truly random i.e. allocation by date of birth, day of the week, medical record number, month of the year, or

(ii) Order in which participants are included in the study was stated as being quasi random.

c) Allocation concealment

(i) *Clearly adequate* if (1) centralised randomisation by telephone, or (2) randomisation schemes were controlled by a pharmacy, use of numbered or coded containers in which capsules looked identical and used numbered bottles administered sequentially, or (3) on-site computer systems which can only be accessed after entering the characteristics of an enrolled participant and allocations were in a locked unreadable file, and (4) sequentially numbered opaque, sealed envelopes.

(ii) *Possibly adequate* if a) sealed envelopes but not sequentially numbered or opaque, or b) a trial in which the description suggested concealment, but other features are suspicious (e.g. markedly unequal control and trial groups; stated random, but unable to obtain further details).
(iii) *Clearly inadequate* when allocation procedure transparent before assignment (e.g. an open list of random numbers, alternation, date of birth, day of week, case record number).

d) Blinding

(i) *Single blind* if the investigator was aware of the treatment/intervention the participant was getting, but the participant was unaware.

(ii) *Double blind* when neither the participants in a trial nor the investigators (and outcome assessors, who might also be the care providers/clinician) were aware of which intervention the participants are given. Trials in which only clinician and patients were blinded were not categorised as double blind.

(iii) *Triple blind* when knowledge of which study participants were in which comparison group was kept secret from the statistician doing the analysis as well as from the study participants and investigators (outcome assessors).

e) Analysis by intention to treat

(i) *Performed* if all the patients in the trial were analysed according to the intervention to which they were allocated, whether they received it or not.

(ii) *Absent* if it was mentioned that participants crossed over treatment group and analysis was not done according to the initial allocation.

(iii) *Not reported* if no mention was made of patients crossing over treatment groups or of the study being done by intention to treat analysis.
2.7 Requesting additional clinical information

Authors of potentially eligible trials were contacted for additional information. Contact details were obtained by:

a) Searching the institutes website to see if any of the authors cited were still at the institute, if unsuccessful then

b) Contacting the head of the department that authors were affiliated to for further information or

c) Sought the assistance of the Cochrane Centres or colleagues in the relevant countries.

Authors were sent a letter explaining the nature of the communication and a request for additional information (a form in which additional information could be filled in was attached to the letter– see Appendix 4).

2.8 Analysis

Analysis was done by using the Review Manager software package of the Cochrane Collaboration (Revman, 2000). Effects were expressed as mean differences or in a meta analysis as weighted mean differences with 95% confidence intervals. A chi-squared test for heterogeneity was used to assess heterogeneity of effects between studies. Significance was set at 0.05. Meta analysis was performed when comparable data from multiple treatments were present with no clinical or statistical heterogeneity.
Subgroup analyses was planned for the following factors:

i) Dosage if different doses of the same drug were studied

ii) Age (less than 12 months, 12 months to 5 years and over 5 years)

iii) Pertussis diagnosed bacteriologically or clinically

iv) Severity of cough [treated in hospital (more severe) vs. ambulatory care (less severe)].

A sensitivity analysis was planned excluding poorer quality studies (unknown or inadequate allocation concealment or quasi-random allocation).
3. RESULTS

3.1 Identification of studies

3.1.1 Electronic searches

Our electronic literature searches produced 1,235 hits i.e. 471 from MEDLINE, 492 from the Cochrane Controlled Trials Register, 25 from the Cochrane Acute Respiratory Infections Trials Register and 247 from LILACS. Twenty-six studies were identified as potentially meeting inclusion criteria after screening the abstracts, and full reports of these studies were examined.

3.1.2 Scanning of reference lists of identified studies

Nineteen additional potentially eligible studies were identified after scanning the reference lists of those studies identified from electronic searches.

3.1.3 Contacts

We contacted ten authors for additional information (see Appendix 3.1). Only one author responded but was unable to provide the information requested as the study was performed ten years previously (1991). Five pharmaceutical companies were contacted (see Appendix 3.2) and four additional potentially eligible studies were identified.

3.1.4 Potentially eligible studies

Forty-nine potentially eligible trials were identified after screening the abstracts and titles. Of these six articles were in Italian, five were in German, two in French, one in Norwegian and one in Chinese.
3.1.5 Included studies

Only 17 trials remained potentially eligible after screening of entire reports. Following closer examination, only nine met the inclusion criteria (Table 1). Analysable data however were extractable from only five reports.

3.1.6 Excluded studies

Eight of the 17 potentially eligible studies were excluded on methodological grounds. Reasons for exclusion of studies are listed in Table 2.

3.1.7 Interventions

The interventions studied in the nine included trials were antihistamines, pertussis immunoglobulin, corticosteroids and salbutamol. Side effects were reported in only three trials. Reports were generally old with the earliest study being published in 1949, three in the 1970's, three in the 1980's and two in the 1990's. The studies were all done in industrialized settings, namely Greece, Sweden (two), Finland, USA, Canada, Italy (two) and New Zealand.

3.2 Methodological quality of included studies

Often 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 nine included studies, two were quasi randomised, six were randomised (four with method of randomisation not stated) and one was a crossover trial. Allocation concealment was clearly adequate in only one study, possibly adequate in four, clearly inadequate in two and not described in two. Six were double blinded, one single blinded (patients only), one patient blinded (receiving placebo) and in one blinding was not reported at all. Three studies
Table 1 Characteristics of included studies

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Methods reported</th>
<th>Participants</th>
<th>Intervention</th>
<th>Outcomes</th>
<th>Allocation Concealment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Danzon 1988</td>
<td>Randomly allocated sequence (table of random numbers controlled by the pharmacy) unknown to the investigator. Done in a double blinded pattern. Intention to treat analysis was not reported. Loss to follow up was unclear.</td>
<td>Inpatients (gender not specified) under 1 yr of age. Vaccination status and previous antibiotic treatment was not reported. Bacteriologically diagnosed pertussis.</td>
<td>Diphenhydramine 5mg/kg/day orally in 3 doses. Side effects were not reported.</td>
<td>Average number of paroxysms of cough over 24 hours (between 25th – 48th hours after starting treatment).</td>
<td>Clearly adequate</td>
</tr>
<tr>
<td>Granstrom 1991</td>
<td>Randomisation done by a computer generated table of random numbers. Was a double-blinded placebo controlled trial. Intention to treat analysis was not reported. 91.8% follow up.</td>
<td>Both male and female inpatients, age range 1.1 - 32.3 months. 51% of the patients had had previous antibiotic treatment but were not previously vaccinated. Clinical, bacteriological or serological diagnosed pertussis.</td>
<td>Specific immunoglobulin treatment, 8ml intramuscularly injected into the buttocks, 2ml 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. Side effects reported were rash in 4.3% of the treatment group; loose stools in 5.3% of the placebo group and pain and swelling at the injection site in 5.3% of the placebo group.</td>
<td>Duration of paroxysms, vomiting, whoop and hospital stay, mean number of paroxysms</td>
<td>Possibly adequate</td>
</tr>
<tr>
<td>Krantz 1985</td>
<td>Generation of randomisation sequence before crossover point not reported. Double-blinded placebo controlled crossover study. Assessor (investigator) was blinded. Patients and observers were blinded to the crossover point. Intention to treat analysis was not reported. 52.9% follow up.</td>
<td>Both male and female inpatients, age range 0.1-2.3 yrs of age. Vaccination status and previous antibiotic treatment was not reported. Had not been given salbutamol within two days of the trial, were monitored according to the protocol and had a confirmed (bacteriological or serological) diagnosis of pertussis.</td>
<td>Salbutamol 0.6mg/kg/day orally in 4 doses for 2 days. Side effects were not reported.</td>
<td>Number of paroxysms of cough, duration of paroxysms</td>
<td>Possibly adequate</td>
</tr>
<tr>
<td>Lucchesi 1949</td>
<td>Quasi random (alternation). Blinding and intention to treat analysis were not reported. Loss to follow up was unclear.</td>
<td>Both male and female inpatients under the age of 1 yr. Vaccination status and previous antibiotic treatment not reported. Clinical and bacteriologically diagnosed pertussis.</td>
<td>Pertussis immune serum, 50 - 100 ml intravenously on admission followed by 50 ml daily until improvement, or 5 doses. Side effects were not reported.</td>
<td>Frequency of paroxysms of cough</td>
<td>Clearly inadequate</td>
</tr>
</tbody>
</table>
Table 1 Characteristics of included studies (continued)

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Methods reported</th>
<th>Participants</th>
<th>Intervention</th>
<th>Outcomes</th>
<th>Allocation Concealment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mertsola 1986</td>
<td>Randomisation method not stated. Was a double-blinded study. Intention to treat analysis was not reported. Loss to follow up was unclear.</td>
<td>Outpatients (gender not specified) with a mean age of 9.4 yrs in the treatment group and 7.5 yrs in the control group. 14.8% received previous antibiotic treatment and all the participants had been previously vaccinated. Bacteriologically and serologically confirmed pertussis.</td>
<td>Salbutamol orally 0.1 mg/kg orally 3 times a day for 10 days. Side effects were not reported.</td>
<td>Number of paroxysms of cough</td>
<td>Not described</td>
</tr>
<tr>
<td>Miraglia 1984</td>
<td>Randomisation method unclear. Was a double blind placebo controlled trial. Intention to treat analysis was not reported. 100% follow up.</td>
<td>Both male and female patients, age range 12 months - 11 yrs in the treatment group and 10 months - 12 yrs in the control group. Vaccination status and previous antibiotic treatment was not reported. Clinically diagnosed pertussis.</td>
<td>Chlorhexidene 1.62 mg/kg/day orally and sobrerol 3.6 mg/kg/day orally. Side effect reported was diarrhoea in 6.7% of the placebo group - author state that this was not related to being apart of the study.</td>
<td>Severity of paroxysms of cough</td>
<td>Possibly adequate</td>
</tr>
<tr>
<td>Pavesio 1977</td>
<td>Randomisation method not stated. Placebo controlled. Intention to treat analysis was not reported. 100 % follow up.</td>
<td>Inpatients (gender not specified), age range 6 months - 3 yrs, coughing for less than 21 days. Not previously vaccinated. Previous antibiotic treatment was not reported. Clinically diagnosed pertussis.</td>
<td>Salbutamol 0.5 mg/kg/day orally in 3 doses for 15 days. No side effects were reported.</td>
<td>Frequency of paroxysms of cough, frequency of whoops</td>
<td>Not described</td>
</tr>
<tr>
<td>Roberts 1992</td>
<td>Randomisation method 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.</td>
<td>Inpatients (gender not specified) less than 6 months of age. Vaccination status and previous antibiotic treatment were not reported. Clinically diagnosed pertussis.</td>
<td>Dexamethasone 0.3mg/kg daily for 4 days. Route of administration not stated. Side effects were not reported.</td>
<td>Percentage paroxysms after 48 hours, duration of hospital stay</td>
<td>Possibly adequate</td>
</tr>
<tr>
<td>Zoumboulakis 1973</td>
<td>Quasi (alternation). Stated that nurse was blinded. Intention to treat analysis was not reported. 94.5% follow up.</td>
<td>Both male and female inpatients coughing for less than three weeks. Age range of 15 days - 3 yrs. 92.7% not previously vaccinated and 7.3% incomplete vaccination. None had previous antibiotic treatment. Clinically diagnosed pertussis.</td>
<td>Hydrocortisone 30mg/kg per day intramuscularly for 2 days followed by a reduced dosage over 6 days. Side effects reported were pulmonary infiltrates in 15.1% of the hydrocortisone group and 10.7% of the control group.</td>
<td>Number of paroxysms of cough, number of whoops, number of vomits</td>
<td>Clearly inadequate</td>
</tr>
</tbody>
</table>
## Table 2 Excluded studies, with reasons for exclusion

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ames 1953</td>
<td>Sampling was reported using the lottery method (implies chance allocation to treatment groups). However we judged the gross baseline imbalances between groups unlikely to be due to be random allocation, and a fatal flaw in validity.</td>
</tr>
<tr>
<td>Badr-El-Din 1976</td>
<td>Stated that patients were randomly subjected to either chloramphenicol or (chloramphenicol and prednisone) or (chloramphenicol and salbutamol). However two chloramphenicol groups were reported with large baseline differences between the two groups and the two treatment groups. No explanation was given for having two chloramphenicol groups.</td>
</tr>
<tr>
<td>Balagtas 1971</td>
<td>Random allocation was abandoned when all patients were immunised during an epidemic, and data for randomly allocated patients was not given. Contacted author to request these data - no response</td>
</tr>
<tr>
<td>Brunskill 1986</td>
<td>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.</td>
</tr>
<tr>
<td>Bruss 1999</td>
<td>Comparison of two doses of pertussis immunoglobulin without comparison with placebo or no treatment.</td>
</tr>
<tr>
<td>Chandra 1972</td>
<td>Method of allocation not stated.</td>
</tr>
<tr>
<td>Lewis 1984</td>
<td>A before - after study with no head - to - head comparison.</td>
</tr>
<tr>
<td>Pavesio 1979</td>
<td>Controlled trial with no random allocation and no mention of methods. Contacted author for clarification - no response</td>
</tr>
</tbody>
</table>
had 100% of the patients included in the final analysis, two greater than 90% of the patients, one with 52.9% of the patients and in three loss to follow was unclear. Intention-to-treat analysis was not reported in any of the nine studies (Table 1). The quality of the reporting of the methods was poor in most studies. Sample sizes for individual studies were small with the largest study having a total sample of 49 patients between treatment and control group and the smallest study nine patients.

3.3 Analysis

We were able to extract data for pre-specified outcomes from nine studies but sufficient data for further analysis from only five. Data were presented as means and standard deviations in reporting of those five studies. For the remainder of the studies we list the summary statistics reported by the authors for our pre-specified outcomes (Table 3).

Suitable data were available for the following interventions:

(i) Antihistamines versus placebo

Diphenhydramine was the only antihistamine studied (Danzon, 1988). Treatment was administered at 5mg/kg/day orally 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 -4.66; 8.64] (Figure 1).
Table 3 Results for pre-specified outcomes reported in included studies in which insufficient raw data were available for further analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Outcomes</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lucchesi 1949</td>
<td>Pertussis immune serum, 50 - 100 ml on admission followed by 50 ml daily until improvement or 5 doses</td>
<td>Frequency of paroxysms of cough</td>
<td>Results were presented graphically as means of seven-day periods with no summary statistic – unable to extract data from the graphs provided. Authors conclusion (from visual inspection of graphs) – &quot;The patients who received serum showed a more regular decline in the rate if frequency of paroxysms when treated in the first week of disease that did the patients in the control group.&quot;</td>
</tr>
<tr>
<td>Pavesio 1977</td>
<td>Salbutamol 0.5 mg/kg/day in 3 doses for 15 days</td>
<td>Frequency of paroxysms of cough, frequency of whoops</td>
<td>Results presented graphically with no summary statistic. Extracted from graphs - N = 50</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean number of daily episodes of cough per 24 hours (day two only)</td>
<td>Mean number of daily episodes of cough per 24 hours (day two only)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Salbutamol</td>
<td>Salbutamol 8.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>Placebo 12.3</td>
</tr>
<tr>
<td>Miraglia 1984</td>
<td>Chlphedianol 1.62 mg/kg/day and sobrelol 3.6 mg/kg/day of</td>
<td>Severity of paroxysms of cough</td>
<td>Semi quantitative score of severity of paroxysms - Scale of 0 – 4, N=15</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Chlphedianol and sobrelol 0.80</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Placebo 1.3</td>
</tr>
<tr>
<td>Zoumboulakis 1973</td>
<td>Hydrocortisone 30mg/kg per day for 2 days followed by a reduced dosage over 6 days</td>
<td>Number of paroxysms of cough, number of whoops, number of vomits</td>
<td>Data presented graphically with no summary statistic - N = 145</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean number of cough per 24 hours (day two only)</td>
<td>Mean number of cough per 24 hours (day two only)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hydrocortisone</td>
<td>Hydrocortisone 16</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No treatment</td>
<td>No treatment 17.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean number of whoop per 24 hours (day two only)</td>
<td>Mean number of whoop per 24 hours (day two only)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hydrocortisone</td>
<td>Hydrocortisone 7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No treatment</td>
<td>No treatment 7.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean number of vomit per 24 hours (day two only)</td>
<td>Mean number of vomit per 24 hours (day two only)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hydrocortisone</td>
<td>Hydrocortisone 4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No treatment</td>
<td>No treatment 4</td>
</tr>
</tbody>
</table>
(ii) Pertussis immunoglobulin versus placebo

Granstrom (1991) conducted a trial assessing the effect of two forms of immunoglobulins raised respectively by an investigational monocomponent toxoid pertussis vaccine and a two component acellular pertussis vaccine. Both treatments were injected intramuscularly (8ml). Since no difference was found between the effects of the two preparations, the results of the two treatment groups were pooled. There was no statistically significant difference in duration of hospital stay, mean decrease of 0.70 days in the treatment group [95%CI -3.79; 2.39] (Figure 2).

**Figure 2   Effect of pertussis immunoglobulin on the duration of hospital stay**

<table>
<thead>
<tr>
<th>Study</th>
<th>Immunoglobulin n</th>
<th>Placebo n</th>
<th>Mean Difference</th>
<th>MD (95%CI Random)</th>
<th>MD (95%CI Random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Granstrom 1991</td>
<td>32</td>
<td>14</td>
<td>-0.70</td>
<td>-0.70 [-3.79, 2.39]</td>
<td></td>
</tr>
</tbody>
</table>


Granstrom (1991) also assessed mean number of whoops and found a borderline statistically significant difference in the mean number of whoops per day in the immunoglobulin groups as compared to the placebo group, mean decrease of 3.10 [95% CI -6.22; 0.02] (Figure 3).

**Figure 3**  Effect of pertussis immunoglobulin on the mean number of whoops per 24 hours

<table>
<thead>
<tr>
<th>Study</th>
<th>Immunoglobulin</th>
<th>Placebo</th>
<th>Mean Difference</th>
<th>MD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Granstrom 1991</td>
<td>33 1.70(3.10)</td>
<td>14 4.80(5.60)</td>
<td>-3.10 [-6.22; 0.02]</td>
<td>-3.10 [-6.22; 0.02]</td>
</tr>
</tbody>
</table>

(iii)  Corticosteroids versus placebo

Robert (1992) assessed the effect of dexamethasone on the duration of hospital stay. Treatment was administered at 0.3mg/kg for four days. Route of administration was not stated. There was no statistically significant difference in duration of hospital stay, mean decrease of 3.45 fewer days in the dexamethasone group [95% CI -15.34; 8.44] (Figure 4).
(iv) Salbutamol versus placebo

Of two studies of salbutamol with extractable data, one was a cross over trial (Krantz 1985) from which we extracted data for the period before the crossover. Treatment was administered at 0.6mg/kg/day orally in four doses for ten days. There was no statistically significant difference in coughing paroxysms, mean decrease of 4.07 coughs per 24 hours in the salbutamol group [95% CI -24.86; 16.72].

Mertsola (1986) conducted a similar study which was a randomised controlled trial. Treatment was administered orally at 0.1mg/kg three times a day for ten days. Again there was no statistically significant difference in coughing paroxysms, mean decrease of 0.74 coughs in the salbutamol group [95% CI -6.18; 4.7].

There was no clinical or statistical heterogeneity (p=0.76) between the two studies. Overall there was no statistically significant difference (p=0.7) in coughing paroxysms, weighted mean decrease of 0.95 coughs per 24 hours in the salbutamol group [95%CI -6.21; 4.31] (Figure 5).
Figure 5  Effects of salbutamol on the number of paroxysms of cough over 24 hours

<table>
<thead>
<tr>
<th>Study</th>
<th>Salbutamol n</th>
<th>mean(sd)</th>
<th>Placebo n</th>
<th>mean(sd)</th>
<th>Mean Difference (95%CI) Fixed</th>
<th>Mean Difference (95%CI Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Krantz 1965</td>
<td>7</td>
<td>7.43(3.95)</td>
<td>2</td>
<td>11.50(14.86)</td>
<td>4.07[-24.86,16.72]</td>
<td>-0.74[-6.18,4.70]</td>
</tr>
<tr>
<td>Mertsola 1986</td>
<td>10</td>
<td>8.56(5.27)</td>
<td>14</td>
<td>9.30(8.30)</td>
<td>-0.95[-6.21,4.31]</td>
<td>-0.95[-6.21,4.31]</td>
</tr>
<tr>
<td>Total</td>
<td>17</td>
<td></td>
<td>16</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity chi-square=0.09  df=1  p=0.76
Test for overall effect z=0.36  p=0.7
4. DISCUSSION

We limited our review to randomised controlled trials because they are widely regarded as the best study design for assessing the effects of interventions. Random allocation minimises the known and unknown imbalances between the study groups and hence controls for confounding (Schulz 2002).

All our interventions were randomised, yet study quality was poor. Even though random allocation is essential to minimise selection bias, it does not guarantee study validity. Benefit from random allocation is dependent on the person enrolling a participant being unaware of which treatment allocation the participant will receive. Inadequate concealment of treatment allocation has been shown empirically to exaggerate the effect of interventions by an average of 41% compared with an exaggeration of 17% for inadequate blinding after allocation (Schulz 1995, Schulz 2002). One study was judged to have had adequate allocation concealment. An intention-to-treat analysis is one in which all the participants in a trial are analysed according to the intervention to which they were allocated, whether they received it or not. Analyses done by intention to treat is important because if patients are analysed in a different treatment group as to the one assigned at the beginning of the trial, the randomisation is no longer valid (Schulz 2002). In this review, none of the trials reported analysis by intention to treat.

Studies were old and poorly reported hence few qualified for inclusion. The potential biases inherent in the studies excluded on methodological grounds
however make their findings questionable, and therefore potentially harmful (Table 2).

We did not pre specify interventions. Doing so would have simplified the review at the cost of potentially excluding an effective intervention that could have been overlooked in current practice. We did explicitly exclude however antibiotics (because the issues of timing of antibiotic administration needs a different approach). The effectiveness of antibiotics will require a systematic review of its own.

No studies of true cough suppressants (e.g. codeine) were identified. This may be because trials done on cough suppressants are not necessarily done with reference to whooping cough.

Studies reported outcomes other than our pre-specified outcomes e.g. duration of cough. We restricted ourselves to the analyses of pre-specified outcomes because of the possibility of differential reporting of significant outcomes. If significant outcomes are more easily reported, inclusion of all reported outcomes carries a high risk of over estimating the effect of interventions. Our choice of pre-specified outcomes aimed to concentrate on those that were clinically meaningful.

No statistically significant effects were found for any of the interventions (except perhaps pertussis immunoglobulin treatment on the mean number of whooops). Examining of the 95% confidence intervals for the effect of this intervention suggests that 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, confidence intervals for the mean differences were wide and sample sizes were small. Thus there were broad ranges for the plausible size of effects of the various interventions. Using diphenhydramine could plausibly result in a decrease of 4.7 paroxysms of cough over 24 hours to an increase of 8.5 paroxysms of cough over 24 hours [95% CI -4.66, 8.46] (Danzon 1988). Similarly pertussis immunoglobulin could decrease hospital stay by 3.8 days or increase it by 2.4 days [95% CI -3.79, 2.39] (Granstrom 1991). Dexamethasone could reduce hospital stay by 15.3 days or increase it by 8.4 [95% CI -15.34, 8.44] (Roberts 1992). Using salbutamol could plausibly result in anything from a decrease in paroxysms of cough by 6.2 over 24 hours to an increase by 4.3 [95% CI -6.21, 4.31] (Krantz 1985, Mertsola 1986). Thus for all these interventions there could be either a clinically meaningful benefit or harm. This indicates that there is insufficient evidence to reach any conclusion. This is not the same as concluding no effect of any of the interventions.

This uncertainty reflects the small number of trials of reliable quality, and the small sample sizes of the better quality trials. Studies did not have the statistical power to show evidence of no effect.

The pre-specified sub group and sensitivity analyses were not feasible because of the small number of uniformly poor quality studies identified.

The studies were done in industrialised countries when pertussis was still relatively common and the understanding of research methodology was more elementary than today. This may partially explain the poor quality and inconclusive nature of the trials. Given improved research methodology and the
fact that the cough in pertussis remains an important clinical problem in developing countries, there is a need for good quality randomised controlled trials of sufficient size to be conducted in developing countries.

5. CONCLUSION

5.1 Reviewers conclusion
a) Many studies of treatments for the cough in whooping cough have been performed but most are of insufficient quality to be valid.
b) Although assessments have been performed on a whole range of interventions, including diphenhyramine, pertussis immunoglobulin, dexamethasone and salbutamol, insufficient evidence exists to draw conclusions about the effects of any of them.

5.2 Implications for practice
The uncertain effectiveness of interventions for the cough in whooping cough should be seen in the context of the potential side effects of the interventions.

5.3 Implications for research
Further good quality randomised controlled trials of adequate statistical power are required to be done in developing countries.

5.4 Potential conflict of interest
None
REFERENCES

Included studies

_Danzon 1988_

_Granstrom 1991_

_Lucchesi 1949_

_Krantz 1985_

_Merstola 1986_

_Miraglia 1984_

_Pavesio 1977_
Roberts 1992

Zoumboulakis 1973

Excluded Studies

Ames 1953

Badr-el-din 1976

Balagtas 1971

Brunskill 1986

Bruss 1999
Chandra 1972

Lewis 1984

Pavesio 1979

Other references

AAP 1997

Bass 1985

Cochrane Collaboration 2002
http://www.cochrane.org/cochrane/general.htm

Cochrane Reviewers Handbook 2001


**Dickersin 1994**


**Easterbrook 1991**


**Egger 1997**


**Feigin 1992**


**Hallander 1999**


**Hewlett 2000**


**Johnston 2000**

Joyce 1998

Long 2000

Mulrow 1987

Otavio 1999
Otavio C, Aldemar CA. Cochrane reviews must use LILACS database like source of articles. Poster presented at the 9th International Cochrane Colloquium, October 2001 Lyon, France.

Paul 1999
Paul N, Lefebvre C. Reports of controlled trials in EMBASE. Poster presented at 2nd Symposium on Systematic Reviews, January 1999, Oxford, UK.

Regina 2000
Regina C. Figueiredo C. LILACS database: eighteen years indexing Latin American and Caribbean health sciences journals. ME/PAHO/WHO, 10th International Conference of Science Editors, August 2000, Rio de Janeiro, Brazil.

Revmann, 2000

Schulz 1995
Schulz 2002

Tinnion 2001

WHO 1999
Appendix 1

Electronic literature search strategies

1. Cochrane Controlled Trials Register
   #1 Pertussis
   #2 Whooping Cough
   #3 #1 OR #2
   #4 Vaccine OR vaccination OR vaccines
   #5 #3 NOT #4

2. Specialised Trials Register (as described by Ron da Souza, trial search coordinator for the Acute Respiratory Infections Group)
   1 All references on the register are coded
   2 Searched by the code 03 for pertussis / whooping cough.
   3 Excluded vaccines and antibiotics
   4 Finally searched for immunoglobulin and whooping cough but found no references not already uncovered by the first search.

3. Medline / Pubmed
   #1 Search whooping cough
   #2 Search pertussis
   #3 Search #1 OR #2
   #4 Search trial or trials
   #5 Search #3 AND #4
   #6 Search #3 AND #4 Limits: Human
#7 Search vaccination OR vaccine OR Vaccines Limits: Human

#8 Search #6 NOT #7 Limits: Human

#9 Search Immunoglobulin OR immunoglobulins Limits: Human

#10 Search #2 AND #9 Limits: Human

#11 #8 OR #10 Limits: Human

4. **LILACS**

1. Whooping Cough
2. OR Pertussis
3. OR Bordetella
4. OR Respiratory
Appendix 2

Whooping Cough Data Extraction Form

STUDY ID: ________________

Reviewer: VP ☐ GS ☐

Authors: ____________________________________________

Journal/yr/vol/iss/pg: ____________________________________________

Title: ____________________________________________

Yes ☐ No ☐

Inclusion criteria

Humans with whooping cough ☐ ☐

Interventions aimed at suppressing whooping cough (reducing cough paroxysms thus includes pertussis immunoglobulin used for treatment of whooping cough but not for prevention) ☐ ☐

Quasi/ alternate or random allocation ☐ ☐

Exclusion criteria

Antibiotics as an intervention (acceptable if both groups receive the same antibiotic) ☐ ☐

Vaccine as an intervention to prevent whooping cough ☐ ☐
Methods

Treatments excluded:__________________________________________________________

Other exclusion criteria:_____________________________________________________

Randomisation method:_____________________________________________________

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quasi-random</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A method of allocating participants to different forms of care that is not truly random; for example, allocation by date of birth, day of the week, medical record number, month of the year, or the order in which participants are included in the study (e.g. alternation).

Allocation concealment

Clearly adequate

Centralised randomisation by telephone; randomisation schemes controlled by a pharmacy; numbered or coded containers in which capsules from identical-looking, numbered bottles are administered sequentially; on-site computer systems which can only be accessed after entering the characteristics of an enrolled participant, where allocations are in a locked unreadable file; and sequentially numbered opaque, sealed envelopes.

Possibly adequate

Sealed envelopes but not sequentially numbered or opaque; a trial in which the description suggests concealment, but other features are suspicious (e.g. markedly unequal controls and trial groups; stated random, but unable to obtain further details).

Clearly inadequate

Any allocation procedure transparent before assignment (e.g. open list of random numbers, alternation, date of birth, day of week, case record number), not stated

Not described

Yes | No
Control Group

Another cough suppressant  

Description:__________________________

Placebo  

Description:__________________________

No treatment  

Other:__________________________

Treatment

<table>
<thead>
<tr>
<th>Description</th>
<th>Intervention (Rx)</th>
<th>Control (Contl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NS - Not Stated  
UN - Unclear  

Route of administration_________________

Other associated treatment in both groups:__________________________
Blinding

Single blind
The investigator is aware of the treatment/intervention the participant is getting, but the participant is unaware.

Double blind
Neither the participants in a trial nor the investigators (outcome assessors, who might also be the care providers/clinician) are aware of which intervention the participants are given. If clinician is blinded and patients- not double blind.

Triple blind
Knowledge of which study participants are in which comparison group is kept secret from the statistician doing the analysis as well as from the study participants and investigators (outcome assessors).

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
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<tbody>
<tr>
<td>Patient</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinician</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assessors</td>
<td></td>
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</tbody>
</table>

Duration of follow-up:________________________

<table>
<thead>
<tr>
<th></th>
<th>Rx</th>
<th>Contl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number randomised</td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Number available to follow-up</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loss to follow-up</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

% of total number randomised included in analysis: __________________________
An intention-to-treat analysis is one in which all the participants in a trial are analysed according to the intervention to which they were allocated, whether they received it or not. If not stated that patients were lost to follow up then it is taken as no ITT.

### Participants

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
<th>Unclear</th>
</tr>
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<tbody>
<tr>
<td>Previously vaccinated</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Description:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous antibiotic treatment:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All participants</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Some (%):</td>
<td></td>
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<td>Male</td>
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Inpatients

Out patients

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<tbody>
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<td>Mean age</td>
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<tr>
<td>Number ≤ 1 year</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Number &gt; 1 year</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Diagnosis**

Bacteriologically / serologically proven □

Clinically diagnosed □

If so, clinical criteria used: 

__________________________________________________________________________

__________________________________________________________________________

Other ___________________________________________________________
## Outcomes

### Categorical

<table>
<thead>
<tr>
<th></th>
<th>No of events per day</th>
<th>No of people at risk</th>
<th>Days on which the outcome was measured</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rx</td>
<td>Contl</td>
<td>Rx</td>
</tr>
<tr>
<td>Paroxysms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whoop</td>
<td></td>
<td></td>
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<tr>
<td>Cyanosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admission to hospital</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of hospital stay</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

**NS** - Not Stated  
**UN** - Unclear

If unable to fit results into this format, please describe briefly.
## Continuous Data

<table>
<thead>
<tr>
<th></th>
<th>Mean SD</th>
<th></th>
<th>Sample size</th>
<th></th>
<th>Days on which the outcome was measured</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Rx</td>
<td>Contl</td>
<td>Rx</td>
</tr>
<tr>
<td>Paroxysms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whoop</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyanosis</td>
<td></td>
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<td></td>
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<td>Duration of hospital stay</td>
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</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

NS - Not Stated
UN - Unclear

If unable to fit results in to this format, please describe briefly.
Yes  No

Adverse effects reported

<table>
<thead>
<tr>
<th>Adverse effects</th>
<th>No of events</th>
<th>No of people at risk</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rx</td>
<td>Contl Rx</td>
<td>Contl</td>
</tr>
<tr>
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</tr>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

No people affected | No people at risk
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Rx</td>
<td>Contl Rx</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total no of effects: ___
Additional information needed from authors

Contacted authors of trial

Date: / / 

Replied

Date: / /
Information provided
Appendix 3

Contacts

3.1  List of authors contacted and their current contact details

Badr El Din 1976
Egypt
Ph: 092034876099.

Chandra 1972 (no contact details for first author)
Dr. YC. Mathur
Niloufer hospital
5 b, Subodaya,
Boggal Kunta
Hyderabad – 500 001
India

Danzon 1988
adanzon@ensp.fr

Granstrom 1991
marta.granstrom@labmed.ki.se

Krantz 1985
kansli@skaraborg-institute.se

Mertsola 1986
jussi.mertsola@utu.fi

Roberts 1992 (no contact details for first author)
d.lennon@auckland.ac.nz

Pavesio 1979 (Author retired)
Ospedale Regina Margherita

Balagtas 1971 (no contact details for first author)
samuel_gotoff@rush.edu.

Zoumboulakis 1973 (no contact details for first author)
Anagnostakis D
Faculty of Medicine
75 Mikras Asias Street
1127 Goudi (2nd floor)
University of Athens
Greece
10551
3.2 List of pharmaceutical companies contacted

1. **Boehringer Ingelheim (PTY) LTD - Silomat**
   Sue Thomas
   Private Bag X3032
   Randburg
   2125
   Tel: +27 11-886 1075
   Fax: +27 11-886 3205
   THOMAS@jnb.boehringer-ingelheim.com

2. **Glaxosmithkline (PTY) LTD – Ventolin, prednisone, betamethasone**
   Navin Singh
   Po Box 3388
   Halfway House
   1685
   Tel: +27 11-313 6000
   Fax: +27 11-313 6111
   ns78966@glaxowellcome.co.uk

3. **Parke-Davis Division Warner Lambert (SA) (PTY) LTD**
   Diphenhydramine
   Annah Amos
   Private Bag X6
   Tokai, 7966
   Tel: 021 710 4111
   Fax: 021 710 4900 / 4008
   Annah.Amos@Pfizer.com

4. **Pharmacia - Hydrocortisone**
   Karen Botha
   P O Box 41111
   Craighall
   2024
   Tel: 011-516 5500
   Fax: 011-516 5618
   Karen.Botha@am.pnu.com

5. **Schering-Plough (PTY) LTD - Dexamethasone**
   Cheryl Goldstone
   P.O.Box 46
   Isando
   1600
   Tel: 011-922 3300
   Fax: 011-974 2977
   Cheryl.goldstone@spcorp.com
Appendix 4

Actual letter sent to an author requesting additional information

8 January 2002

Dear Prof Gotoff

We were very interested to read your article RE: *Balagtas Rolando C, Nelson Kenrad E, Levin Stuart, Gotoff Samuel P, Treatment of pertussis with pertussis immune globulin, The Journal of Pediatrics, 1971 August, Pg 203 - 208*

You may be aware of the Cochrane Collaboration, a world-wide collaboration with the goals of preparing, maintaining and making accessible up-to-date systematic reviews of the effects of health care. We are currently undertaking a Cochrane systematic review for "The Symptomatic Treatment Of The Cough In Whooping Cough". I am writing on behalf of our collaborative team regarding the your article cited above.

We would like to include this important study in a meta-analysis with other similar studies that we have also identified. However, some of the information we would need to do this is not available from the article. We would be grateful if you could provide us with the information requested below on the attached form.

**Extra Information:**

1. a. How were patients allocated to intervention and control group? E.g. tossing a coin, computer generates list of random number, by date of birth, day of week, clinical judgement etc.

   b. Allocation concealment - was the person enrolling a participant unaware of which treatment allocation the participant will receive, until the participant was irrevocably enrolled. Who knew the code/sequence of treatment being allocated? What was the method of allocation during the measles epidemic?

   c. To which groups were the two-drop outs allocated.

   d. Blinding - Keeping the treatment assignment secret from the study participants or investigators. Was the clinician blinded?
2. Sample size, means and standard deviations for each group for any of the following outcomes and at what days/times they were measured. We are particularly interested in the data collected before the epidemic.

- Frequency of paroxysms of cough
- Frequency of vomiting
- Frequency of whoops

3. Age - also the distribution of age for each group would be helpful.

Other Studies:

As part of the review we need to perform as complete a literature search as possible. As you are an expert in the field we would be very grateful if you could let us know of any further trials on the symptomatic treatment of the cough in whooping cough of which you are aware, whether published or unpublished, completed or in progress. I have attached a list of trials already identified. Please check list before naming other trials to prevent repetition.

In the meantime I would be delighted to answer any questions you have about our review. I enclose a copy of our protocol. If you require any information about the Cochrane Collaboration feel free to contact me or you can visit our website at http://www.cochrane.org

If there are other personnel from your study whom it would be more appropriate for us to contact (for example, the person who holds the data), please send me their contact details or forward this and any subsequent letters to them.

Please respond within 14 days of receiving this letter, as we are waiting for your data to complete our analysis. Also, if data is not available please inform us within 14 days of receiving this letter.

Thank you in advance.

Yours sincerely,

Victoria Pillay  
South African Cochrane Centre  
Medical Research Council  
PO Box 19070  
Tygerberg  
South Africa  
Tel: +27 21 9380 834  
Fax: +27 21 9380 836  
E-mail: victoria.pillay@mrc.ac.za
Information Required

1. a. How were patients allocated to intervention and control group e.g. tossing a coin, computer generates list of random number, by date of birth, day of week, clinical judgement etc (please describe below).

________________________________________________________________________
________________________________________________________________________
________________________________________________________________________
________________________________________________________________________

b. Allocation concealment - was the person enrolling a participant unaware of which treatment allocation the participant will receive, until the participant was irrevocably enrolled (please tick the correct box).

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
</table>

If yes, please describe what measures were taken to achieve this.

________________________________________________________________________
________________________________________________________________________
________________________________________________________________________
________________________________________________________________________

Who knew the code/sequence of treatment being allocated?

________________________________________________________________________
________________________________________________________________________
What was the method of allocation during the measles epidemic?

________________________________________________________________________
________________________________________________________________________
________________________________________________________________________
________________________________________________________________________

C. Which group were the two dropouts allocated to, number of patients lost to follow up in each group and duration of follow up (please fill in the number of patients for each category)?

<table>
<thead>
<tr>
<th></th>
<th>Intervention</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excluded patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total number randomised</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loss to follow up</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number available</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

D. Blinding - Was the treatment assignment kept secret from the following group (please tick the correct box).

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinicians</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
2. Sample size, means and standard deviations for each group for any of the following outcomes and at what days/times they were measured. We are interested in information collected before the measles epidemic.

<table>
<thead>
<tr>
<th></th>
<th>Intervention</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sample Size</td>
<td>Means</td>
</tr>
<tr>
<td>Paroxysms of cough</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whoops</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* SD = Standard Deviation

3. Age - also the distribution of age for each group would be helpful (please fill in the number of patients for each category).

<table>
<thead>
<tr>
<th></th>
<th>Intervention</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number ≤ 1yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number &gt; 1yr</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Other Studies:

Any further trials on the symptomatic treatment of the cough in whooping cough of which you are aware, whether published or unpublished, completed or in progress.