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Foxwell AR, Cripps AW, Dear KBG

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[Intervention Review]

Haemophilus influenzae oral whole cell vaccination for preventing acute exacerbations of chronic bronchitis

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ABSTRACT

Background

Acute bronchitis leading to ongoing exacerbations is a serious condition predisposed to by viruses, bacteria or environmental factors. It can be fatal. Antibiotic therapy is not particularly useful. An oral *Haemophilus influenzae* vaccine has been developed.

Objectives

To assess the effects of an oral, monobacterial whole-cell, killed, nontypeable *H. influenzae* vaccine in protecting against recurrent acute episodes in chronic bronchitis.

Search methods

In this updated review, we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* Issue 1, 2006), MEDLINE (1966 to January Week 4 2006), EMBASE (1990 to September 2005) and ISI Current Contents (2004 to May 2006).

Selection criteria

Randomised controlled trials (RCTs) comparing the effects of the *H. influenzae* vaccine on patients with recurrent acute exacerbations of chronic bronchitis were included when there was overt matching of the vaccine and placebo groups on clinical grounds.

Data collection and analysis

Three authors extracted data and assessed trial quality independently from original records and publications for incidence and severity of bronchitis episodes and carriage rate of nontypeable *H. influenzae* measured in the upper respiratory tract every three months following vaccination.

Main results

Six trials were included in the study with a total of 440 participants. The vaccine reduced the incidence of bronchitic episodes at three months after vaccination (rate ratio is 0.69; 95% CI 0.41 to 1.14) and at six months after vaccination (rate ratio 0.82; 95% CI 0.62 to 1.09). If these results been statistically significant, they would have represented a reduction in acute bronchitic attacks for vaccinated individuals of 31% at three months, and 18% at six. The effect had disappeared by nine months.

Haemophilus influenzae oral whole cell vaccination for preventing acute exacerbations of chronic bronchitis (Review)

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The severity of exacerbations in the treatment group, as measured by requirement to prescribe antibiotics, was likewise reduced by 58% at three months (Peto odds ratio = 0.42; 95% CI 0.16 to 1.13), and by 65% at six months (Peto odds ratio = 0.35; 95% CI 0.16 to 0.75).

Authors' conclusions

Vaccinating patients with recurrent acute exacerbations of chronic bronchitis in the autumn may reduce the number and severity of exacerbations over the following winter. A large clinical trial is needed.

PLAIN LANGUAGE SUMMARY

Vaccination against acute exacerbations of chronic bronchitis in autumn may reduce the number and severity of attacks during winter

Acute attacks of bronchitis often increase in frequency and severity during winter, especially among people who have chronic obstructive pulmonary disease (COPD) or chronic bronchitis. These attacks are commonly associated with nontypeable *Haemophilus influenzae*. The oral vaccine described in this review is of particular interest because it decreases carriage of nontypeable *Haemophilus influenzae* in the upper respiratory tract. The review of trials found that people with COPD or chronic bronchitis who were orally immunised in autumn had a not significant trend to fewer and less severe attacks of bronchitis during the following winter.

BACKGROUND

Acute exacerbations of bronchitis and chronic obstructive pulmonary disease often occur in people with compromised respiratory function. The aetiology of the exacerbations remains a matter of debate with viruses, bacteria and environmental pollutants being found to be definitive causative agents (Szilasi 2006). The bacterial agents responsible for the acute exacerbations are commonly an expansion of the patient's own respiratory tract microbiota often following the arrival of a new strain of normal commensal (Sethi 2002). The bacterial cause often reflects a particular balance of the host-parasite relationship involving an expanded bacterial flora within the bronchus lumen (Sapey 2006). Nontypeable *Haemophilus influenzae* (*H. influenzae*) is of particular importance because it is the most commonly isolated bacterium at times of exacerbation (Eldika 2006).

In patients with chronic bronchitis and established obstructive lung disease, acute exacerbations of infection are a major cause of morbidity and mortality, being the 4th most common global cause of adult mortality (Barnes 2004) and predicted to be the 3rd most common cause by 2020 (Lopez 1998). The inflammatory outburst resulting from exacerbation often leads to lung function decline, skeletal muscle wasting and hospital admission (Sapey 2006; Szilasi 2006).

Various treatment strategies have been attempted including immunostimulatory agents made from bacterial extracts, such as

OM-85 BV and antibiotics. While OM-85 BV appears not to affect the occurrence of acute exacerbations of bronchitis, it does decrease the severity of the exacerbation (Collet 1997). Conventional antibiotic therapy is not very helpful, perhaps because of a lack of ability to clear colonisers such as nontypeable *H. influenzae* from the airways (Foxwell 1998; Murphy 1992; Van Alphen 1995).

An alternative treatment strategy is mucosal immunisation. Successful vaccines for infections caused by *H. influenzae* (Hib) depend on immunity stimulated against the type-specific polysaccharide capsule of Hib. But this is not effective against infections caused by organisms lacking the polysaccharide, such as nontypeable *H. influenzae*. To address this, oral whole-cell nontypeable *H. influenzae* vaccine has been developed to prevent nontypeable *H. influenzae* infections.

A series of clinical trials were conducted between 1983 and 1988 of oral immunisation against nontypeable *H. influenzae* T1-83 Newcastle (Clancy 1985); T2- 86 Newcastle (Clancy 1990); T3- 86 Newcastle (Clancy 1992); T4- 87 Newcastle (Clancy 1992); T5- 87 Goroka, PNG (Lehmann 1991); T6- 88 Perth (Tandon 1991)) to investigate prevention of exacerbations of chronic bronchitis. The outcomes of these trials have been varied.

We systematically evaluated the effects of protecting against recurrent episodes of bronchitis in an attempt to clarify if further study is required in this area. This is particularly important given what

appears to be new activity in oral whole killed cell immunisation against respiratory infection (Cripps 2006; Foxwell 2003; Malley 2005; Sedlak-Weinstein 2005) and the potential of this immunisation strategy to have broad application at lower cost.

OBJECTIVES

The objectives of this review are:

1. to determine the effectiveness of an oral whole cell nontypeable *H. influenzae* vaccine in protecting against recurrent episodes of bronchitis;
2. to determine the relationship between vaccine efficacy and respiratory tract carriage of nontypeable *H. influenzae*.

METHODS

Criteria for considering studies for this review

Types of studies

All RCTs comparing the effects of an oral monobacterial nontypeable *H. influenzae* vaccine on people predisposed to acute exacerbations of chronic bronchitis, with age-matched individuals receiving a placebo control.

Types of participants

All studies dealing with adults with either chronic obstructive pulmonary disease or recurrent acute exacerbations of chronic bronchitis. As these conditions have been closely associated with high numbers of nontypeable *H. influenzae*, the vaccine was considered to be relevant in looking at prevention of exacerbation frequency and severity.

Types of interventions

All trials comparing a monobacterial nontypeable *H. influenzae* orally administered vaccine with a lactose placebo were included. Trials allowed the use of bronchodilators, analgesics and antibiotics to both active and placebo groups.

Types of outcome measures

The main outcomes of interest were:

1. incidence of acute exacerbations of chronic bronchitis;
2. carriage level of nontypeable *H. influenzae* in the respiratory tract;

3. numbers of prescriptions for antibiotics in the trial and follow up periods as an indication of severity of acute exacerbations.

Search methods for identification of studies

In the first update of this review published in Issue 3, 2003, we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* Issue 1, 2003); MEDLINE (1966 to 2003); EMBASE (1990 to 2003); ExtraMED (1994 to 2003); ISI Current Contents (1993 to 2003); Carl Uncover (1988 to 2003) and contacted investigators of the studies.

CENTRAL was searched, using similar search terms as those used to search MEDLINE. An electronic search was also conducted on EMBASE (1990 to 2003); ExtraMED (1994 to 2003); ISI Current Contents (1993 to 2003); and Carl Uncover (1988 to 2003). Manual data were sought by searching reference lists of trials and review articles; searching books related to respiratory tract infections, mucosal immunology or vaccines; searching abstracts from respiratory tract conferences, immunology conferences, microbiology conferences or vaccine conferences; and written enquiries to the authors of major relevant studies and experts in the field.

In this 2006 updated review we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* Issue 1, 2006), MEDLINE (1966 to January Week 4 2006), EMBASE (1990 to September 2005) and ISI Current Contents (2004 to May 2006). The following search strategy was used to search MEDLINE. See Appendices for CENTRAL and EMBASE search strategies.

MEDLINE (OVID)

1 exp Haemophilus influenzae/

2 exp Vaccines/

3 and/1-2

4 exp Haemophilus Vaccines/

5 (hemophilus adj influenz\$ adj5 (vaccin\$ or immuni\$)).mp.

6 (haemophilus adj influenz\$ adj5 (vaccin\$ or immuni\$)).mp.

7 or/3-6

8 exp Bronchitis/

9 bronchit\$.mp.

10 or/8-9

11 7 and 10

Data collection and analysis

Two authors (RF, AC) independently selected the trials using the methods section of the study and without reference to the results, authors or journals. The methodological quality was assessed by/ from details of randomisation, particularly with regards to the pre-trial period and the number of patients lost to follow up. Disagreements were solved by discussion. No assumptions have been made that have not been statistically tested for by the authors

of the original clinical trials. The ratio of males to females in each trial was very similar between the vaccinated and placebo groups. No attempt was made to ask whether the vaccine was better for one sex or the other. Similarly, no attempt has been made to distinguish between cultural backgrounds or the optimal age group for response to the vaccine. While these questions would be good to address, the lack of data across all the trials precludes analysis. All analyses were performed based on 'intention to treat', with further information being sought from authors of original studies when necessary. Each outcome measure compared between vaccinated and placebo groups was assessed for heterogeneity (the likelihood of the observed differences being due to a factor other than chance alone), using the Review Manager (RevMan) software. Numbers needed to treat (NNT - the number of patients who need to be treated to prevent 1 adverse outcome) were calculated as the reciprocal of the rate difference as an overall outcome of all six trials at three months.

The outcomes (01) "Episodes of acute bronchitis" is a count variable, and was analysed using the "generic inverse variance" method of RevMan. For each trial, the data entered were the natural logarithm of the rate ratio (negative values favouring vaccination) and its standard error. These values were derived outside RevMan, by fitting Poisson regression models in Stata using the number of patients as the exposure measure. Clustering of episodes within patients and varying months of observation due to drop outs were ignored due to the necessary data being unavailable. Outcome 02 "Carriage of nontypeable *Haemophilus influenzae*" and 03 "Numbers of prescriptions for antibiotics in the trial and follow up periods as an indication of severity of acute exacerbations" are binary outcomes and were analysed directly as such in RevMan.

RESULTS

Description of studies

There were six clinical trials that tested the efficacy of the vaccine in patients prone to recurrent acute exacerbations of chronic bronchitis, (see *Included Studies* and *Excluded Studies Tables*). The vaccine preparation and immunisation regime used in all trials consisted of three courses of 10 to the 11th power numbers of formalin-killed *H. influenzae* in enteric-coated tablets taken on days 0, 28 and 56. Each course consisted of two tablets taken after breakfast over three consecutive days. In all trials, the placebo groups took enteric-coated tablets containing glucose.

The trials varied in their length from three to 12 months duration. A pharmacist preparing bottles of either active or placebo tablets achieved randomisation of all the trials. These bottles were numbered and randomised before being distributed to the clinicians involved in the trials. The pharmacist was responsible for breaking the randomised code at the conclusion of the trial period.

Trials varied slightly in their population groups: trials 1, 2, 3, 4 and 6 were taken from chronic bronchitics in Australia, with mean ages of 42 to 71 years. Trial five was conducted in chronic bronchitics in Papua New Guinea, with a mean age of 51 years. Trial one also had a lower rate of acute bronchitic episodes than the remaining included trials.

Bacterial load was assessed by a standardised method throughout the six trials. Multiple cultures were performed on each person. In normal circumstances, the first culture following vaccination was taken at three months. Cultures were taken at regular three monthly intervals and extra cultures taken during illness. The method of obtaining the samples, transporting material and culture methods followed a set protocol. The only difference between the trials was in the method used to record the results, with absolute count and quadrant methods being used. Future trials should standardise all aspects of the measurement of bacterial load.

Measured outcomes in the trials were varied but included bacterial load within the respiratory tract, the number and severity of acute exacerbations and the usage of antibiotics. These outcomes were not always statistically useful.

Corticosteroids were administered at a similar rate in both active and placebo groups. Antibiotics were prescribed in both arms of the trial according to standard clinical criteria. These included increase in volume and purulence of sputum, usually with increased breathlessness and sometimes fever. Standards were tight as the clinicians involved in the trials were following established procedures for respiratory medicine in Australia.

The Glasgow study (T7- 87 Glasgow) had to be excluded because of a serious imbalance in the randomised distribution of the incidence of acute exacerbations of bronchitis between incidence and control. The trial has been poorly documented and we have been unable to recover raw data for the trial.

Risk of bias in included studies

The trials in this study were all RCTs and fell into category B. Following the pre-trial period in trials 1 to 6, patients were stratified for age, sex and attack rate for bronchitic episodes. A pharmacist randomly numbered placebo and active preparations before they were sent to clinicians involved with dispensing the preparations to trial participants. It was not until completion of the trial period that the pharmacist provided the list to allow decoding of the preparations and comparison with the data collected from the participants.

Effects of interventions

The total number of participants in the six included trials amount to 440. All participants were either male or female and aged between 19 and 93 years. They all had either chronic obstructive pulmonary disease, or recurrent acute exacerbations of chronic

bronchitis. Patients were grouped and either treated with a placebo or a regime of whole cell killed preparations of nontypeable *H. influenzae*.

I. Incidence of acute exacerbations of chronic bronchitis

The number of acute bronchitic episodes at zero to three months shows considerable between-study heterogeneity, with study T1 (T1-83 Newcastle) having a markedly lower rate ratio (higher vaccine efficacy) than the later four studies. The heterogeneity for meta-analysis is set at P value = 0.1 and thus there is a statistically significance (P value = 0.06) to justify using a random-effects model to allow for it. The pooled rate ratio is then 0.69 (95% CI 0.42 to 1.14) which is not significantly different from 1 (P value = 0.15). Omitting study T1 (T1-83 Newcastle) eliminates the heterogeneity (now P value = 0.92) and moderates the pooled estimate to 0.83 (95% CI 0.61 to 1.12), P value = 0.21. However, there is no biological reason to exclude this study and when including all six studies, the results demonstrate 31% less acute bronchitic episodes in vaccinated individuals at three months.

Study T1 did not provide data beyond three months. The pooled estimate of the other studies over zero to six months, including T2 (T2- 86 Newcastle) which provided no data at three months, is very similar to zero to three months: no heterogeneity (P value = 0.18), estimated rate ratio 0.82 (95% CI 0.61 to 1.09), P value = 0.17.

In terms of the number of people needing to be vaccinated for prevention of a single episode, the data can be interpreted as follows. The estimated rate ratio including all available studies is 0.69 (95% CI 0.42 to 1.14) for zero to three months following vaccination. If one assumes a background rate of 0.6 episodes per person, this translates to a reduction of one episode for every five persons vaccinated and perhaps one episode for every three persons vaccinated (estimate 5.4, lower confidence limit 2.9).

2. Carriage level of nontypeable *H. influenzae* in the respiratory tract

Carriage of nontypeable *H. influenzae* was 32% lower in the treatment group at three months (Peto odds ratio = 0.68; 95% CI 0.41 to 1.11) and 43% lower in the treatment group at six months (Peto odds ratio = 0.57; 95% CI 0.32 to 1.03). It returned to a similar level between the treatment and control group by nine months following vaccination

3. Numbers of prescriptions for antibiotics in the trial and follow up periods as an indication of severity of acute exacerbations

The severity of exacerbations, as measured by the requirement to prescribe antibiotics, also favoured the treatment group at three

months, with a 58% reduction in antibiotic usage (Peto odds ratio = 0.42; 95% CI 0.16 to 1.13) and at six months with a 65% reduction in antibiotic usage (Peto odds ratio = 0.35; 95% CI 0.16 to 0.75) following vaccination.

DISCUSSION

This review analysed six trials of monobacterial, whole-killed cell nontypeable *H. influenzae* vaccine in cases of multiple acute exacerbations of chronic bronchitis. The results demonstrate efficacy at a level of 20 to 30% and biologically support the use of the vaccine in reducing the number and severity of exacerbations within three to six months of vaccination.

Most of the studies were conducted with vaccination beginning in the autumn and thus reducing the exacerbations of bronchitis over winter. It would appear that the vaccine was not long-lasting, with the control and treatment groups having similar incidence of exacerbations 9 to 12 months following vaccination. If bronchitics with repeated exacerbations were to use this vaccine, at present the statistics show that a temporary reprieve from exacerbations would occur during winter.

The protocols used in the trials lack consistency in length of the trials, and thus, data at 9 months and 12 months following vaccination could only be extracted from two trials. There was doubt as to the ability to match people in the control and treatment groups for infectious episodes at the beginning of the trials. Many of the confidence intervals were wide due to the low numbers of reported incidences for data, such as patients requiring prescription of antibiotics. Data were also difficult to compare between trials due to the methods of reporting. This was particularly true when attempting to glean information on seasonal variability and the severity of exacerbations. These may be the reasons there was marked heterogeneity between studies. Consequently, it is recommended further trials be conducted using larger groups than in any of the single trials currently reviewed.

AUTHORS' CONCLUSIONS

Implications for practice

Vaccination of patients with recurrent acute exacerbations of chronic bronchitis who are vaccinated in the autumn may reduce the number and severity of exacerbations over the winter months. With realistic assumptions on background rates of bronchitic episodes, the results suggest that one episode of bronchitis may be prevented for every five individuals vaccinated. These results may be related to the higher level of bacterial colonisation during winter and care needs to be taken in presuming that the vaccine would be effective over a year.

Implications for research

There needs to be a large clinical trial into the long-term effects of monobacterial whole-killed cell non-typeable *H. influenzae* vaccine. It would be useful for this trial to assess both the outcome at 12 months and two years following vaccination.

The first trial had a higher attack rate than the subsequent trials and the vaccine group appeared to respond a lot more strongly to the vaccine than subsequent trials. Careful standardisation of the protocols (in terms of outcome measures) in the areas of numbers of infectious episodes, severity of exacerbations, usage of antibiotics and carriage level of nontypeable *H. influenzae* needs to be addressed.

The concept of oral immunisation against nontypeable *H. influenzae* infection is worthy of further study. Broncho-Vascom (OM Pharma, Switzerland), a product containing lyophilised extracts of a number of bacteria, including *H. influenzae*, has been demon-

strated to be efficacious through either reducing the number of acute upper respiratory tract infections or reducing the severity of acute bronchitic exacerbations in a number of infection situations where nontypeable *H. influenzae* is acknowledged as one of the causative agents. However, these studies have not been accompanied by any comprehensive bacteriology to demonstrate the effect of this preparation on nontypeable *H. influenzae* respiratory tract carriage.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

T1-83 Newcastle

Methods	Randomised, double-blind, prospective, placebo-controlled study of three months duration over winter	
Participants	50 patients with chronic obstructive lung disease. 16 given placebo without sodium tauroglycocholate, 17 given placebo with sodium tauroglycocholate, 17 vaccinated. Mean age 62, sex ratio (m/f) 16/1 for the placebo group and 64.7, sex ratio 14/3 for the vaccine group. Many took antibiotics and bronchodilators. Assume no drop-outs	
Interventions	Vaccine consisting of 10 to the 11th formalin killed nontypeable Haemophilus influenzae in 3 courses of enteric coated tablets given at days 0, 28 and 56. Each course consisted of two tablets given over three consecutive days before breakfast. Placebos were enteric coated glucose tablets with or without sodium tauroglycocholate	
Outcomes	No significant difference was found between placebo groups taking enteric coated tablets with or without sodium tauroglycocholate; therefore the two placebo groups were combined for the purpose of this study. Authors demonstrated that the vaccine resulted in a 10-fold reduction in infection at 3 months post-immunisation. This protection was not significant one year later. Their appeared to be no correlation between clinical protection and the amount of H. influenzae carriage	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

T2- 86 Newcastle

Methods	Randomised, double-blind, placebo-controlled study of six months duration including winter	
Participants	40 patients with chronic bronchitis. 3 withdrawals, 2 from placebo and 1 from active treatment group. 20 given a placebo, 20 vaccinated. Mean age 46.3, sex ratio (m/f) 8/12 for the placebo group and 47.4, sex ratio 11/9 for the vaccine group	
Interventions	Vaccine consisting of 10 to the 11th formalin killed nontypeable Haemophilus influenzae in 3 courses of enteric coated tablets given at days 0, 28 and 56. Each course consisted of two tablets given over three consecutive days before breakfast. Placebos were enteric coated glucose tablets	
Outcomes	Authors stated that the vaccine resulted in a marked reduction in the total number of episodes of acute bronchitis and acute wheezy bronchitis concomitant with a reduction in antibiotic use. They also warned that the small group number and a possible favouring of the vaccine group might have occurred. They also demonstrated a prevention of increase of H. influenzae colonization in the vaccinated group	

T2- 86 Newcastle (Continued)

Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

T3- 86 Newcastle

Methods	Randomised, double-blind, placebo-controlled study of 12 months duration starting in March	
Participants	109 patients with chronic bronchitis. 55 given a placebo, 54 vaccinated. Mean age 66.8, sex ratio (m/f) 44/11 for the placebo group and 64.5, sex ratio 41/13 for the vaccine group	
Interventions	Vaccine consisting of 10 to the 11th formalin killed nontypeable Haemophilus influenzae in 3 courses of enteric coated tablets given at days 0, 28 and 56. Each course consisted of two tablets given over three consecutive days before breakfast. Placebos were enteric coated glucose tablets	
Outcomes	Authors noted that there was no significant reduction of acute bronchitic episodes in patients who had low levels of H. influenzae colonisation. A reduction in colonisation levels was noted	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

T4- 87 Newcastle

Methods	Randomised, double-blind, placebo-controlled study of 12 months duration starting in March
Participants	102 patients with chronic bronchitis. 49 given a placebo, 53 vaccinated. Mean age 64.2, sex ratio (m/f) 37/12 for the placebo group and 65.8, sex ratio 43/10 for the vaccine group
Interventions	Vaccine consisting of 10 to the 11th formalin killed nontypeable Haemophilus influenzae in 3 courses of enteric coated tablets given at days 0, 28 and 56. Each course consisted of two tablets given over three consecutive days before breakfast. Placebos were enteric coated glucose tablets
Outcomes	Authors noted that there was a significant 'treatment effect' in patients who had low levels of H. influenzae colonisation. A reduction in colonisation levels was noted
Notes	
<i>Risk of bias</i>	

T4- 87 Newcastle (Continued)

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

T5- 87 Goroka, PNG

Methods	Randomised, double-blind, prospective placebo-controlled study of 12 months duration starting in October
Participants	62 patients with chronic bronchitis or more than 2 episodes of acute bronchitis in 2 years. 32 given a placebo, 30 vaccinated. Mean age 53.7, sex ratio (m/f) 15/17 for the placebo group and 52.6, sex ratio 15/17 for the vaccine group: Drop-outs were 11 from vaccine group and 4 from placebo group
Interventions	Vaccine consisting of 10 to the 11th formalin killed nontypeable Haemophilus influenzae in 3 courses of enteric coated tablets given at days 0, 28 and 56. Each course consisted of two tablets given over three consecutive days before breakfast. Placebos were enteric coated glucose tablets
Outcomes	Authors demonstrated that the vaccine group had significantly lower acute bronchitic episodes post vaccination than the control group in individuals who had less severe but not severe disease. The carriage rate of H. influenzae also declined in the vaccinated group
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

T6- 88 Perth

Methods	Randomised, double-blind, placebo-controlled study of 12 months duration starting in March
Participants	77 patients with chronic bronchitis. 10 were withdrawn (7 in placebo group and 3 in vaccine group). 3 from the vaccine group died. 33 given a placebo, 31 vaccinated. Mean age 71.1, sex ratio (m/f) 30/3 for the placebo group and 73.1, sex ratio 22/9 for the vaccine group
Interventions	Vaccine consisting of 10 to the 11th formalin killed nontypeable Haemophilus influenzae in 3 courses of enteric coated tablets given at days 0, 28 and 56. Each course consisted of two tablets given over three consecutive days before breakfast. Placebos were enteric coated glucose tablets
Outcomes	Authors demonstrated a reduction in acute bronchitic episodes in patients who received the vaccine. They also needed to prescribe fewer antibiotics despite the number of individual's requiring antibiotics being similar. A reduction in H. influenzae colonization also occurred in vaccinated individuals
Notes	

T6- 88 Perth (Continued)

<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
T7- 87 Glasgow	The Glasgow study (T7 - 87) was the only study where the active and placebo groups were not randomised with respect to incidence of acute exacerbations of bronchitis and as a result a serious imbalance occurred between the arms of the trial. The trial had been poorly documented and we were unable to recover raw data for the trial. It is the opinion of the reviewers these factors represent a terminal flaw and (T7 - 87) has been excluded from the analysis for this reason. Addendum: the results are not published and the only data available is through confidential files with Cortecs Pty Ltd

DATA AND ANALYSES

Comparison 1. Vaccine versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Episodes of acute bronchitis	6		Rate ratio (Random, 95% CI)	0.78 [0.61, 1.00]
1.1 3 months	5		Rate ratio (Random, 95% CI)	0.69 [0.42, 1.14]
1.2 6 months	5		Rate ratio (Random, 95% CI)	0.82 [0.61, 1.09]
2 Carriage of nontypeable <i>Haemophilus influenzae</i>	5		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
2.1 3 months	5	360	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.68 [0.41, 1.11]
2.2 6 months	3	210	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.57 [0.32, 1.03]
2.3 9 months	2	211	Peto Odds Ratio (Peto, Fixed, 95% CI)	8.09 [2.07, 31.59]
3 Number of patients receiving antibiotics	2		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
3.1 3 months	1	64	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.42 [0.16, 1.13]
3.2 6 months	2	101	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.35 [0.16, 0.75]

Analysis 1.1. Comparison 1 Vaccine versus control, Outcome 1 Episodes of acute bronchitis.

Review: Haemophilus influenzae oral whole cell vaccination for preventing acute exacerbations of chronic bronchitis

Comparison: 1 Vaccine versus control

Outcome: 1 Episodes of acute bronchitis

(Continued ...)

Analysis 1.2. Comparison 1 Vaccine versus control, Outcome 2 Carriage of nontypeable Haemophilus influenzae.

Review: Haemophilus influenzae oral whole cell vaccination for preventing acute exacerbations of chronic bronchitis

Comparison: 1 Vaccine versus control

Outcome: 2 Carriage of nontypeable Haemophilus influenzae

Analysis 1.3. Comparison 1 Vaccine versus control, Outcome 3 Number of patients receiving antibiotics.

Review: Haemophilus influenzae oral whole cell vaccination for preventing acute exacerbations of chronic bronchitis

Comparison: 1 Vaccine versus control

Outcome: 3 Number of patients receiving antibiotics

APPENDICES

Appendix 1. CENTRAL search strategy

- #1 explode 'Haemophilus-influenzae' / all subheadings in MIME,MJME
- #2 explode 'Vaccines-' / all subheadings in MIME,MJME
- #3 #1 and #2
- #4 explode 'Haemophilus-Vaccines' / all subheadings in MIME,MJME
- #5 (h?emophilus adj influenz*) near vaccin*
- #6 #3 or #4 or #5
- #7 explode 'Bronchitis-' / all subheadings in MIME,MJME
- #8 explode 'Bronchitis-Chronic' / all subheadings in MIME,MJME
- #9 bronchit*
- #10 #7 or #8 or #9
- #11 #6 and #10

Appendix 2. EMBASE search strategy

EMBASE (WebSpirs) was searched using the following strategy.

#1 explode 'Haemophilus-influenzae' / all subheadings in DEM,DER,DRM,DRR

#2 explode 'vaccine-' / all subheadings in DEM,DER,DRM,DRR

#3 #1 and #2 (328 records)

#4 explode 'Haemophilus-vaccine' / all subheadings in DEM,DER,DRM,DRR

#5 hemophilus influenz* and (vaccin* or immuni*)

#6 haemophilus influenz* and (vaccin* or immuni*)

#7 #3 or #4 or #5 or #6

#8 explode 'bronchitis-' / all subheadings in DEM,DER,DRM,DRR

#9 (bronchit* in ti) or (bronchit* in ab)

#10 #8 or #9

#11 #7 and #10

FEEDBACK

Haemophilus influenzae oral vaccination

Summary

I was concerned about the reporting, analysis and interpretation of the results of the included studies. Specifically the problems I noted were:

1. The numerical values in the abstract don't seem to tally with those in the Forest plot. I'm not sure that giving the WMD to 3 decimal places is justified.
2. What exactly do the numerical values of the WMD difference represent. Is it really infectious episodes? Values in the 20's and 30's in the 3 month follow-up don't seem compatible with this.
3. Is the meta-analysis correct? The chi-square value is astronomical - the analysis needs to be checked.
4. The conclusions need to reflect the variation in results with some studies being favourable and some unfavourable. It is not clear to me that the vaccine is effective from the data presented.

Hope these brief observations help improve the review.

I certify that I have no affiliations with or involvement in any organisation or entity with a direct financial interest in the subject matter of my criticisms.

Reply

Response from authors.

The comments made relate to the first issue of this review published in Issue 1, 2001. Since the original publication all the statistics have been verified and clarified. The most instructive response is in the translation of the results into clinical practice, particularly in relation to the frequency of exacerbations and the ability to reduce exacerbations for three months following the taking of the oral vaccine.

As noted in the review, the estimated rate ratio is 0.666 (95% CI 0.500 to 0.887) for zero to three months after vaccination. Assuming a background rate of 0.6 episodes per person, this translates to a reduction of about one episode for every five persons vaccinated (95% CI 3.3 to 14.7). Over zero to six months the estimated rate ratio is less extreme and is not statistically significant at 0.83 (95% CI .67 to 1.03). The background rate is higher, however, at about one episode per person in the first six months, and the number needed to treat is about six persons vaccinated to prevent one episode (95% CI 3 to infinity). The implication for zero to three months vaccination has now been included in the results section with a comment also inserted in the 'Implication for practice'.

Ruth Foxwell

Allan Cripps

Keith Dear

Contributors

Chris Hyde (21/09/2000)

WHAT'S NEW

Last assessed as up-to-date: 2 July 2006.

Date	Event	Description
14 April 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 3, 1998

Review first published: Issue 1, 2000

Date	Event	Description
2 February 2006	New search has been performed	Searched conducted.
14 March 2003	New search has been performed	Searched conducted. Review reinstated issue 3, 2003
6 November 2000	Amended	This review was withdrawn after comments were received pointing out inconsistencies between the data and the text. The reviewers are currently working on revisions
27 October 1998	New search has been performed	Review first published Issue 3, 1998

CONTRIBUTIONS OF AUTHORS

AR Foxwell and AW Cripps provided expert opinion on the literature, inclusion and statistical analysis of the vaccine trials. KBG Dear provided expert opinion on statistical analysis of the vaccine trials and their meta-analysis. All three authors contributed to the analysis of data and writing of the review.

DECLARATIONS OF INTEREST

Professor Allan Cripps was involved in the initial animal work and conduct of the four trials in Newcastle, Australia. He is not employed by the commercialising company, has not received honoraria or participated in expert testimony on behalf of the commercialising company. However, he has undertaken a consultancy and had a small stock ownership in the commercialising company. The commercial product, 'Bronchostat', which was derived from the clinical trials assessed, is no longer commercially available.

NOTES

This review was withdrawn after comments were received pointing out inconsistencies between the data and the text. The reviewers completed their revisions and the review was re-published in Issue 3, 2003.

Editors' note:

The Acute Respiratory Infections Group would like to thank Kristine Clement for reading and commenting on this review.

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Oral; Bronchitis [*prevention & control]; Chronic Disease; Haemophilus Vaccines [*administration & dosage]; Randomized Controlled Trials as Topic; Seasons; Secondary Prevention

MeSH check words

Humans