Haemophilus influenzae oral vaccination for preventing acute exacerbations of chronic bronchitis and chronic obstructive pulmonary disease (Review)

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[Intervention Review]

Haemophilus influenzae oral vaccination for preventing acute exacerbations of chronic bronchitis and chronic obstructive pulmonary disease

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ABSTRACT

Background

Chronic bronchitis and chronic obstructive pulmonary disease (COPD) are serious conditions in which patients are predisposed to viral and bacterial infections resulting in potentially fatal acute exacerbations. COPD is defined as a lung disease characterised by obstruction to lung airflow that interferes with normal breathing. Antibiotic therapy has not been particularly useful in eradicating bacteria such as non-typeable *Haemophilus influenzae* (NTHi) because they are naturally occurring flora of the upper respiratory tract in many people. However, they can cause opportunistic infection. An oral NTHi vaccine has been developed to protect against recurrent infective acute exacerbations in chronic bronchitis.

Objectives

To assess the effectiveness of an oral, whole-cell, non-typeable *H. influenzae* (NTHi) vaccine in protecting against recurrent episodes of acute exacerbations of chronic bronchitis and COPD in adults. To assess the effectiveness of NTHi vaccine in reducing NTHi colonising the respiratory tract during recurrent episodes of acute exacerbations of COPD.

Search methods

We searched the following databases: CENTRAL (2014, Issue 6), MEDLINE (1946 to July week 3, 2014), EMBASE (1974 to July 2014), CINAHL (1981 to July 2014), LILACS (1982 to July 2014) and Web of Science (1955 to July 2014). We also searched trials registries and contacted authors of trials requesting unpublished data.

Selection criteria

We included randomised controlled trials comparing the effects of an oral monobacterial NTHi vaccine in adults with recurrent acute exacerbations of chronic bronchitis or COPD when there was overt matching of the vaccine and placebo groups on clinical grounds. The selection criteria considered populations aged less than 65 years and those older than 65 years.

Data collection and analysis

Two authors independently assessed trial quality and extracted data from original records and publications for incidence and severity of bronchitis episodes and carriage rate of NTHi measured in the upper respiratory tract, as well as data relevant to other primary and secondary outcomes.

Main results

We identified six placebo-controlled randomised controlled trials with a total of 557 participants. They investigated the efficacy of enteric-coated, killed preparations of *H. influenzae* in populations prone to recurrent acute exacerbations of chronic bronchitis or COPD. The vaccine preparation and immunisation regime in all trials consisted of at least three courses of formalin-killed *H. influenzae* in enteric-coated tablets taken at intervals (for example, days 0, 28 and 56). Each course generally consisted of two tablets taken after breakfast over three consecutive days. In all cases the placebo groups took enteric-coated tablets containing glucose. Risk of bias was moderate across the studies, namely due to the lack of information provided about methods and inadequate presentation of results.

Meta-analysis of the oral NTHi vaccine showed a small, non-statistically significant reduction in the incidence of acute exacerbations of chronic bronchitis or COPD by 2.048% (risk ratio (RR) 0.97, 95% confidence interval (CI) 0.84 to 1.12, P value = 0.68). There was no significant difference in mortality rate between the vaccine and placebo groups (odds ratio (OR) 1.62, 95% CI 0.63 to 4.12, P value = 0.31).

We were unable to meta-analyse the carriage levels of NTHi in participants as each trial reported this result using different units and tools of measurement. Four trials showed no significant difference in carriage levels, while two trials showed a significant decrease in carriage levels in the vaccinated group compared with placebo.

Four trials assessed severity of exacerbations measured by requirement for antibiotics. Three of these trials were comparable and when meta-analysed showed a statistically significant 80% increase in antibiotic courses per person in the placebo group (RR 1.81, 95% CI 1.35 to 2.44, P value < 0.0001). There was no significant difference between the groups with regards to hospital admission rates (OR 0.96, 95% CI 0.13 to 7.04, P value = 0.97). Adverse events were reported in all six trials with a point estimate suggestive that they occurred more frequently in the vaccine group, however, this result was not statistically significant (RR 1.43, 95% CI 0.70 to 2.92, P value = 0.87). Quality of life was not meta-analysed but was reported in two trials, with results at six months showing an improvement in quality of life in the vaccinated group (scoring at least two points better than placebo).

Authors' conclusions

Analyses demonstrate that NTHi oral vaccination of patients with recurrent exacerbations of chronic bronchitis or COPD does not yield a significant reduction in the number and severity of exacerbations. Evidence is mixed and the individual trials that show a significant benefit of the vaccine are too small to advocate widespread oral vaccination of people with COPD.

PLAIN LANGUAGE SUMMARY

Haemophilus influenzae oral vaccination for preventing acute exacerbations of chronic bronchitis and chronic obstructive pulmonary disease

Review question

We reviewed the evidence about the effect of a non-typeable *Haemophilus influenzae* (*H. influenzae*) (NTHi) vaccine in preventing repeated *H. influenzae* infections in people with chronic obstructive pulmonary disease (COPD) or chronic bronchitis.

Background

People with COPD can often have frequent infections that worsen symptoms of their lung disease, that is increased breathlessness, purulent discharge and decompensating oxygen saturations levels, known as an 'acute exacerbation'. The most common bacteria that causes this is *H. influenzae*; it can lead to hospitalisation and sometimes death. If these infections can be prevented with a vaccine, people with COPD may have improved outcomes compared to the current practice of treating infections as they arise.

Study characteristics

The evidence is current to July 2014. We identified six studies with 557 participants. The studies were blinded, placebo-controlled randomised trials that tested how effective the NTHi vaccine is in preventing infections in people aged over 18 years with COPD or

chronic bronchitis. In all six trials, both the vaccine and placebo group were given at least three courses of tablets at regular intervals over a period of three to 12 months. Generally the baseline demographics of participants across the included studies shared similar characteristics (such as diet, lifestyle and living conditions) to other high-income countries. Ages ranged between 40 and 80 years. The studies counted the number of infections the participants experienced, levels of respiratory tract bacteria, deaths, side effects, hospital admissions or treatment with antibiotics.

Key results

The NTHi vaccine has no significant impact on reducing the number of infections COPD patients experience. There was no significant difference in mortality rate between the vaccine and placebo groups and the reported deaths in the vaccinated group were not attributed to the vaccine.

The levels of *H. influenzae* bacteria found in the respiratory tracts of participants was not significantly different between the vaccine and placebo groups. Due to inconsistencies of measurement between the trials, we were not able to compare the studies against one another.

Antibiotics, which can be an indicator of severe infection, were significantly more commonly prescribed in the placebo group. Evidence of hospital admissions showed that there was no difference in the likelihood of being hospitalised in either the vaccine or placebo group. Two trials studying quality of life found that vaccinated participants generally had a better quality of life, but these results were measured differently and so could not be compared.

Adverse effects were not reported nor clearly defined amongst the trials. Five trials reported adverse effects but there was no particular association with either the vaccine or placebo group. Further research is needed to define adverse effects as outcome measures for more definitive analyses regarding vaccine side effects.

Quality of the evidence

The studies were well conducted with moderate risk of bias. The main limitation of this review was the lack of consistency regarding the definitions and outcome measures among the individual studies, which affected the overall synthesis and interpretation of the results. Fewer participants may cause the results to be more likely to be affected by chance. One trial had more participants than the other five combined and it contributed more to the final analysis. There was moderate heterogeneity (the studies show quite different results) when this study was included in the analysis, especially in numbers of infections. However, the results are consistent and do not change if this study is removed from the analysis.

Conclusion

We concluded after reviewing the relevant studies that the *H. influenzae* vaccine taken orally in people with chronic bronchitis and COPD does not have a significant reduction in the number and severity of acute exacerbations.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Haemophilus influenzae oral vaccination for prevention of acute exacerbations of chronic bronchitis and chronic obstructive pulmonary disease (COPD)

Patient or population: adults (> 18 years of age) with either COPD or recurrent acute exacerbations of chronic bronchitis
Settings: community and outpatients
Intervention: oral monobacterial vaccination with killed NTHi
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk *Not vaccinated*	Corresponding risk *NTHi oral vaccinated*				
Acute exacerbations (number of exacerbations/person/year)	**2.111 exacerbations per person/year**	**1.633 exacerbations per person/year**	**RR 0.97 (0.84 to 1.12)**	557 (6)	⊕⊕◯◯ **low**[1]	Despite an absolute estimated decrease in the rate of exacerbations in the vaccinated group, the result is negligible (95% CI crosses 1.00) and not statistically significant (P value = 0.68)
Mortality (deaths during trial period)	**23 per 1000**	**37 per 1000** (15 to 88)	**OR 1.62 (0.63 to 4.12)**	518 (5)	⊕◯◯◯ **very low**[2]	Despite more absolute deaths occurring in the vaccinated group, the result is negligible (95% CI crosses 1.00) and not statistically significant (P value = 0.31). Deaths were not necessarily attributed to the use of the vaccine

Carriage of NTHi *Not meta-analysed*	N/A	N/A	N/A	N/A	⊕○○○ **very low**[6]	We were unable to meta-analyse the carriage levels of NTHi in participants as each trial reported this result using different units and tools of measurement. 4 trials showed no significant difference in carriage levels, while 2 trials showed a significant decrease in carriage levels in the vaccinated group compared with the placebo group
Antibiotic prescriptions (number of courses/person/year) ***Corticosteroids not meta-analysed*	**6.198 prescriptions per person/year**	**3.162 prescriptions per person/year**	**RR 1.81 (1.35 to 2.44)**	142 (3)	⊕⊕○○ **low**[3]	Courses of antibiotics were found to be prescribed in the placebo group at a rate approximately 80% greater than the vaccinated group (P value <0.0001) (Please note that a RR > 1.0 here indicates more antibiotics being prescribed to participants in the placebo group; that is, RR 1.81 corresponds to an approximately 80% increased rate of antibiotic prescriptions when not receiving the vaccine. The placebo group is being compared to the vaccine in this instance to

						attempt to demonstrate how many more antibiotics are required in those not vaccinated) **2*studies reported corticosteroid use, however due to differences in units of measurement, these results could not be meta-analysed*
Hospital admissions (number of patients hospitalised during trial period)	**311 per 1000**	**466 per 1000** (359 to 570)	**OR 0.96 (0.13 to 7.04)**	358 (2)	⊕⊕⊕○ **moderate**[4]	The difference in the likelihood of being hospitalised was found to be negligible (95% CI crosses 1.00) between the 2 groups (P value = 0.01) (Significant heterogeneity was also noted with this result (I^2 = 84%) ; there may be unknown and unmeasured factors contributing to hospitalisations; we used the random-effects model for analysis here, versus the fixed-effect model for non-heterogenous data)
Adverse events (number of adverse events/person/year)	**0.319 adverse events per person/year**	**0.430 adverse events per person/year**	**RR 1.43 (0.70 to 2.92)**	484 (4)	⊕⊕○○ **low**[5]	Despite an estimated absolute increased rate of adverse events in the vaccinated group, the result is negligible (95% CI crosses 1.00) and not statistically significant (P value = 0.61). Adverse

						events were not necessarily attributable to the vaccine
Quality of life *Not meta-analysed*	N/A	N/A	N/A	N/A	⊕◯◯◯ **very low**[6]	Quality of life was not meta-analysed due to differing units of measurement, but was reported in 2 trials, which showed an improvement at 6 months in the vaccine group (scoring at least 2 points better than the placebo group; significance unknown)

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

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]One study had marked heterogeneity; most studies had a low number of participants; one study had significant attrition.
[2]Mortality was not formally measured; five studies reported on deaths but none attributed to vaccine.
[3]Only three studies recorded information on prescriptions; studies had a low number of participants; method of allocation concealment and randomisation was unclear in two of the studies.
[4]Only two studies recorded information of hospitalisations; one study was significantly larger than the other.
[5]Most studies had a low number of participants; one study may have had attrition bias; two studies had high risk of bias for randomisation and allocation concealment.
[6]Meta-analysis was not performed; inconsistent units of measurement used by studies, therefore not comparable.

BACKGROUND

Description of the condition

Chronic obstructive pulmonary disease (COPD) is characterised by persistent airflow limitation that is progressive and associated with an enhanced chronic inflammatory response. The chronic airflow limitation characteristic of COPD is caused by a mixture of small airways disease (obstructive bronchiolitis) and gas-exchange impediment through parenchymal destruction (emphysema). The changes associated with an inflammatory response include cellular infiltrate, mucus secretion and structural remodelling, which diminishes the overall ability of the airways to remain patent during expiration. This limitation in airflow, as a measurement of disease severity, is best measured and assessed by spirometry (COPD is defined as the forced expiratory volume in one second (FEV_1) being lower than 80% of the predicted normal) (GOLD 2011; Otczyk 2011).

Chronic bronchitis is defined clinically by the presence of cough and sputum production for at least three months in each of two consecutive years. It is an independent disease entity which may precede or follow the development of airflow limitation and may be associated with development and/or acceleration of fixed airflow limitation, that is, COPD. Chronic bronchitis may exist in patients with normal spirometry (GOLD 2011). While patients can remain undiagnosed and have no clinical evidence of a lung disease until they present with advanced COPD, many have a history of symptomatic disease, evidenced as chronic cough and sputum (chronic bronchitis) and/or recurrent episodes of acute wheezy bronchitis and/or late onset reversible airways disease (intrinsic asthma). Currently, the diagnosis of an acute exacerbation is based entirely on clinical presentation. There is no consensus regarding an objective measurement of an exacerbation (GOLD 2011). The relationship between these entities is complex and not well understood, with no obligatory linkage with COPD but has the capacity to progress to COPD (Otczyk 2011).

An acute exacerbation is defined as an acute event characterised by worsening of the patient's respiratory symptoms beyond normal daily variations and can lead to a change in medication (GOLD 2011). The best predictors of exacerbations are a history of previously treated exacerbations and worsening airflow limitation (GOLD 2011). They may be triggered by bacterial or viral infection (or both simultaneously), environmental pollutants or as yet undetermined factors. The characteristic response is increased inflammation resulting in increased purulent sputum production, hyperinflation and gas trapping, with reduced expiratory flow, thus accounting for the dyspnoea associated with these episodes (GOLD 2011). Whilst participants with an atopic constitution (hypersensitive to allergens) may have a predisposition to develop COPD, it should be recognised that bacterial colonisation of damaged airways plays an important pathogenic role. In participants with established obstructive lung disease, acute attacks of infection are a major cause of morbidity and mortality.

The GOLD guidelines estimate the prevalence of COPD to range from 7.8% to 19.7% of the population worldwide (GOLD 2011). COPD is very prominent in populations of smokers and ex-smokers. However, estimates of prevalence in people who have never smoked range from 3% to 11% (GOLD 2011). The World Health Organization (WHO) estimates 5% of all deaths globally can be attributed to COPD, with the disease becoming the third leading cause of death by 2030 (WHO 2013). Whilst epidemiological information regarding COPD comes from high-income countries, 90% of COPD deaths occur in low and middle-income countries (WHO 2013).

The management of acute exacerbations focuses on treating triggers (including infections) and relieving symptoms with bronchodilators, glucocorticoids and antibiotics. Prevention of further exacerbations focuses on vaccination of influenza and pneumococcus strains (WHO 2013). A recent Cochrane review on the use of prophylactic antibiotics for COPD exacerbations concluded there was a reduction in the number of patients experiencing exacerbations with continuous macrolide antibiotic use. The number needed to treat to prevent one exacerbation was eight. These promising findings need to be weighed against the risks from long-term antibiotic use such as side effects of medications and bacterial resistance (Herath 2013).

Bacterial and viral causative agents have been identified and may coexist in a benign or pathogenic capacity; because of this, the specific microbiological aetiology of acute exacerbations in chronic bronchitis and COPD patients remains a matter of debate. The pathogens responsible for these acute exacerbations are often found in the participant's upper respiratory tract and (opportunistic) infections are caused by an upset in the balance of the host-parasite relationship. Bacterial colonisation is most common and more severe compared to viral infections. The upper respiratory tract is commonly home to *Staphylococcus epidermidis* (*S. epidermidis*),*Staphylococcus aureus* (*S. aureus*),*Streptococcus pneumoniae* (*S. pneumoniae*),*Streptococcus pyogenes* (*S. pyogenes*),*H. influenzae* and*Neisseria meningitides* (*N. meningitides*). The lower respiratory tract is normally virtually free of micro-organisms, due to physiological clearance mechanisms (e.g. mucociliary clearance). However, should these systems become damaged (as is the case in COPD or bronchitis patients), pathogens such as non-typeable *H. influenzae* (NTHi) or *Pseudomonas aeruginosa* (*P. aeruginosa*) are usually the ones to colonise these sites (Butt 1990). NTHi is of particular importance in this scenario because of its frequent and predominant pattern of mucosal colonisation of the respiratory tract. Higher levels of Immunoglobulin E (IgE) have been detected in the serum of patients with COPD and it has been observed that NTHi triggers histamine release. This process occurs through both IgE- and non-IgE-dependent mechanisms from cells contained within the respiratory mucosal sensitised to the bacterium. These findings demonstrate that NTHi may also play a role in the

development of the reversible component of airways obstruction in COPD. Immediate hypersensitivity via IgE anti-bacterial antibodies to colonising bacteria may contribute to bronchial disease progression and severity (Otczyk 2011). As these conditions have been associated with high numbers of NTHi, the vaccine was considered to be relevant in prevention of exacerbation frequency and severity.

Description of the intervention

Various treatment strategies have been attempted including immuno-stimulatory 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 reduces the severity of the exacerbation (55% less total days of hospitalisation compared to placebo) (Collet 1997). Conventional antibiotic therapy has not been particularly helpful, possibly due to the inability to effectively clear respiratory flora such as NTHi that leads to further growth and sepsis (Foxwell 1998; Murphy 1992; Van Alphen 1995). Recent studies have identified a role for antibiotics in the treatment of COPD (Albert 2011; Macfarlane 2001). Although significant differences in the incidence of exacerbation were noted between groups, the long-term effect on microbial resistance was not reported. This underscores the importance of exploring vaccination as a prophylactic treatment of COPD.

An alternative strategy is mucosal immunisation. Successful vaccines for *H. influenzae* depend on immunity stimulation against the type-specific polysaccharide capsule of *Haemophilus influenzae B* (Hib). Following the development of successful vaccines for infections caused by Hib, attention is now focused on developing a vaccine for NTHi. Accordingly, an oral, whole-cell NTHi vaccine has been developed to prevent NTHi infections, which is the focus of this review.

Oral immunisation reduced bacterial loads in participants who were chronically colonised and NTHi-specific cellular responses were detected in white blood cells (lymphocytes) in the serum (Otczyk 2010). This suggests that a NTHi vaccine may be useful as it demonstrates that mucosal immunisation can be used therapeutically to enhance or modify an immune response to improve the outcomes of an established chronic mucosal infection (Otczyk 2010).

How the intervention might work

The vaccine is believed to be most effectively absorbed through the gastrointestinal tract in order to trigger an immune response. The killed NTHi cells of the vaccine are coated with formalin to protect it from gastric degradation, thus enabling it to access the M-cells of the gut mucosal immune system through pattern-recognition receptors that are designed to identify pathogen-associated molecular patterns (i.e. PRR-PAMP interactions). Human and animal studies support the hypothesis that oral NTHi immunisation stimulates T-cells in the Peyers patches of the gastrointestinal tract (Foxwell 1998). The T-cells, upon stimulation from the vaccine, migrate to the respiratory system via afferent lymphatics and blood, where they are further stimulated by bacteria in the bronchial mucosa. Cytokines are secreted from the stimulated T-cells to further increase immune activity. This results in increased recruitment and up-regulation of neutrophil white blood cells into the bronchial space, which in turn assists in clearing bacteria through phagocytosis and thus reducing the bacterial load (Clancy 2011).

However, it is to be noted that this form of immunisation does not trigger classical mucosal Immunoglobulin A (IgA) responses but rather by the means outlined above. Nonetheless, an oral vaccine of inactivated NTHi makes use of a 'physiological protective loop' to improve airway immune function. The vaccine is consumed orally and digested within the gastrointestinal tract, which triggers an innate immune response in the respiratory tract. Through a specific activation of immune cells (in the gastrointestinal tract) this initiates non-specific protection (in the airways). Pathways that stimulate T-helper 17 immune cells responsible for airway protection then generate an increased white blood cell responsiveness to all pathogens in the respiratory tract (Clancy 2011).

Why it is important to do this review

COPD is a major cause of morbidity and mortality. Acute exacerbations of COPD reflect intense intrabronchial inflammation, where recurrent exacerbations are linked to worsening of airflow obstruction and health status of the individual. Acute exacerbations of COPD can be fatal. Recent studies demonstrate that oral immunotherapy with NTHi reduces the level of bacterial colonisation in the airways as well as the incidence and severity of acute exacerbations (Otczyk 2011).

Chronic antibiotic therapy is not particularly feasible, so an oral, whole-cell vaccination for NTHi has been developed to reduce morbidity and mortality in participants at risk. Clinical benefit has been reflected in reduced incidence and severity of exacerbations in a number of studies. A review of trials that use oral NTHi whole-cell vaccinations should evaluate if oral immunotherapy provides a significant therapeutic advance in limiting damage in COPD and may highlight the pathogenic role of bacterial colonisation of damaged airways.

This is an update of a Cochrane Review first published in 1998 and last updated in 2006 (Foxwell 2006). The previous authors concluded that participants with recurrent bronchitis vaccinated in the autumn have a decreased incidence and severity of their exacerbations during winter.

OBJECTIVES

To assess the effectiveness of an oral, whole-cell, non-typeable *H. influenzae* (NTHi) vaccine in protecting against recurrent episodes of acute exacerbations of chronic bronchitis and COPD in adults.
To assess the effectiveness of NTHi vaccine in reducing NTHi colonising the respiratory tract during recurrent episodes of acute exacerbations of COPD.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) investigating the efficacy of an oral monobacterial NTHi vaccine in people predisposed to acute exacerbations of chronic bronchitis and COPD.

Types of participants

Adults (18 years or older) with either COPD or recurrent acute exacerbations of chronic bronchitis.

Types of interventions

All trials comparing a monobacterial NTHi orally administered vaccine with a placebo. Trials may allow the use of bronchodilators, analgesics and antibiotics to both active and placebo groups.

Types of outcome measures

Primary outcomes

1. Incidence of acute exacerbations of chronic bronchitis or COPD.
2. Mortality.

Secondary outcomes

1. Carriage level of NTHi in the respiratory tract (including nasopharyngeal swabs, sputum samples, nasopharyngeal aspirates).
2. Numbers of prescriptions for antibiotics and corticosteroids in the trial and follow-up periods (including hospital admissions) as an indication of severity of acute exacerbations.
3. Any associated adverse side effects from the NTHi vaccination, measurable from symptomology and participant reports.
4. Quality of life. A validated tool measurement was required for trials to be included in this review.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (2014, Issue 6), which includes the Acute Respiratory Infections Group's Specialised Register, MEDLINE (1946 to July week 3, 2014), EMBASE (1974 to July 2014), CINAHL (1981 to July 2014), LILACS (1985 to July 2014) and Web of Science (1955 to July 2014).
We used the search strategy in Appendix 1 to search MEDLINE and CENTRAL. We combined the MEDLINE search with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity-maximising version (2008 revision); Ovid format (Lefebvre 2011). We adapted the search strategy to search EMBASE (see Appendix 2), CINAHL (see Appendix 3), LILACS (see Appendix 4) and Web of Science (see Appendix 5). We used no publication or language restrictions.

Searching other resources

We searched the clinical trials registers, WHO International Clinical Trials Registry Platform (ICTRP) (http://www.who.int/ictrp/en/) and ClinicalTrials.gov (http://clinicaltrials.gov/) for completed and ongoing trials (last searched 29 July 2014). We also searched reference lists of included trials and review studies; books related to respiratory tract infections, mucosal immunology or vaccines; abstracts from respiratory conferences, immunology conferences, microbiology conferences or vaccine conferences; and sent written enquiries to the authors of major relevant studies and experts in the field. We also contacted pharmaceutical companies to obtain access to unpublished trials.

Data collection and analysis

Selection of studies

Two review authors (KL, ET) assessed titles and abstracts retrieved from the search to determine their relevance concerning the objectives of this review. We managed disagreements through discussion and/or a deciding arbiter (MVD). We entered all search results into Review Manager 5.2 (RevMan 2012).

Data extraction and management

Two review authors (HH, SNP) designed a data extraction sheet for trial reports, which was pilot tested using sample studies and revised by the other authors. Two review authors (HH, SNP) then independently extracted data from the reports. We extracted data from each report separately and then combined data in the event of multiple reports for the same study. We managed disagreements through discussion and/or a deciding arbiter (MVD).

Assessment of risk of bias in included studies

Two review authors (KL, JP) independently analysed each trial in conjunction with The Cochrane Collaboration's table for assessing 'Risk of bias' (Higgins 2011; RevMan 2014): sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other potential threats to validity are domains that we judged each study on. Review authors' judgements involved rating the risk of bias for each domain as "high" or "low" or "unclear" whilst providing supporting information that led to that rating. We managed disagreements through discussion and/or a deciding arbiter (MVD).

Measures of treatment effect

1. We presented dichotomous (binary) data as a measure of risk and relative risk by using an odds ratio (OR) or risk ratio (RR) with 95% confidence intervals (CIs). We calculated the absolute risk reduction (ARR) for consumer comparison against other treatments or non-treatment.
2. We presented continuous data as mean differences (MDs) if the same scale was used or as standardised mean differences (SMDs) if different scales were used with a standard deviation (SD) of the estimate.
3. We looked for quality of life (QoL) outcomes as measured in the included studies. Quality of life measurements had to be measured using a validated tool. If possible, we pooled these outcomes but if not, we discussed and summarised them.
4. We have pooled data reported as rates by using the inverse variance method as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Unit of analysis issues

The unit of analysis in our review is the participant.

Dealing with missing data

We contacted the trial authors of the original studies when further data or information was required. We performed analyses based on intention-to-treat (ITT), such that we assumed missing data for randomised participants to be treatment failures in this review. This ITT analysis may underestimate the effect of the intervention, therefore we performed both ITT and on-treatment analyses to explore the impact of missing data on the overall outcome. We presented the findings of these analyses in the Discussion section.

Assessment of heterogeneity

We assessed included trials for heterogeneity (which is a variation in study outcomes amongst the studies as further defined in Higgins 2011) through two successive steps to determine if they should be pooled with the rest of the included trials or reported in a systematic review.

1. Two review authors (KL, JP) independently analysed trials for their 'face-value' similarities: that is, for clinical diversity (participants, interventions and outcomes) and methodological diversity (study design and risk of bias).
2. We subsequently assessed trials for statistical heterogeneity using the Chi^2 test with a P value of less than 0.10 being statistically significant. We calculated the I^2 statistic as instructed in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011; RevMan 2014). If this was greater than 50% we considered the pooled trials to be significantly heterogeneous.

Assessment of reporting biases

If a sufficient number of studies had been pooled (i.e. greater than 25), we planned to use a funnel plot to visually inspect the risk of publication bias, where more pronounced asymmetry of the funnel plot may be indicative of a substantial overestimation of the intervention effect (Higgins 2011; RevMan 2014).

Data synthesis

We synthesised the data as follows.

1. We used a fixed-effect model for binary or continuous data in the absence of statistical heterogeneity ($I^2 < 50\%$) according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011; RevMan 2014).
2. We used a random-effects model for binary or continuous data in the presence of statistical heterogeneity ($I^2 > 50\%$) for pooling the trial data using the Mantel-Haenszel method according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011; RevMan 2014). This model of analysis will make the assumption that the studies are not measuring for the same intervention effect, but instead will consequently estimate for an overall intervention effect that is trending amongst the studies.
3. We also used the fixed-effect model to pool study data that reported events as rates according to the *Cochrane Handbook for Systematic Reviews of Interventions*; only fixed-effect meta-analysis methods are available in RevMan for 'O - E and Variance' outcome (Higgins 2011; RevMan 2014).

Subgroup analysis and investigation of heterogeneity

If sufficient data were available, we planned to explore specific subgroups for further analyses of treatment effect.

1. Comparison of continued-smoking versus ex-smoking populations.
2. Younger (< 65 years) versus older (65 years and older) participants.

Sensitivity analysis

If sufficient data were available, we planned to perform sensitivity analyses by:

1. examining how the addition of high risk of bias studies to low risk of bias studies impacts on the overall outcome to determine the effects of risk of bias; and

2. examining which studies contribute to heterogeneity and how this impacts on the overall outcome.

We used different methods of pooling, e.g. initially pooling all trials and then excluding one-by-one specific trials from the meta-analysis and comparing the results, whilst also comparing the use of a fixed-effect versus random-effects model for the pooling analysis. Otherwise, we entered trials one-by-one into the meta-analysis to assess the robustness of the pooled estimates.

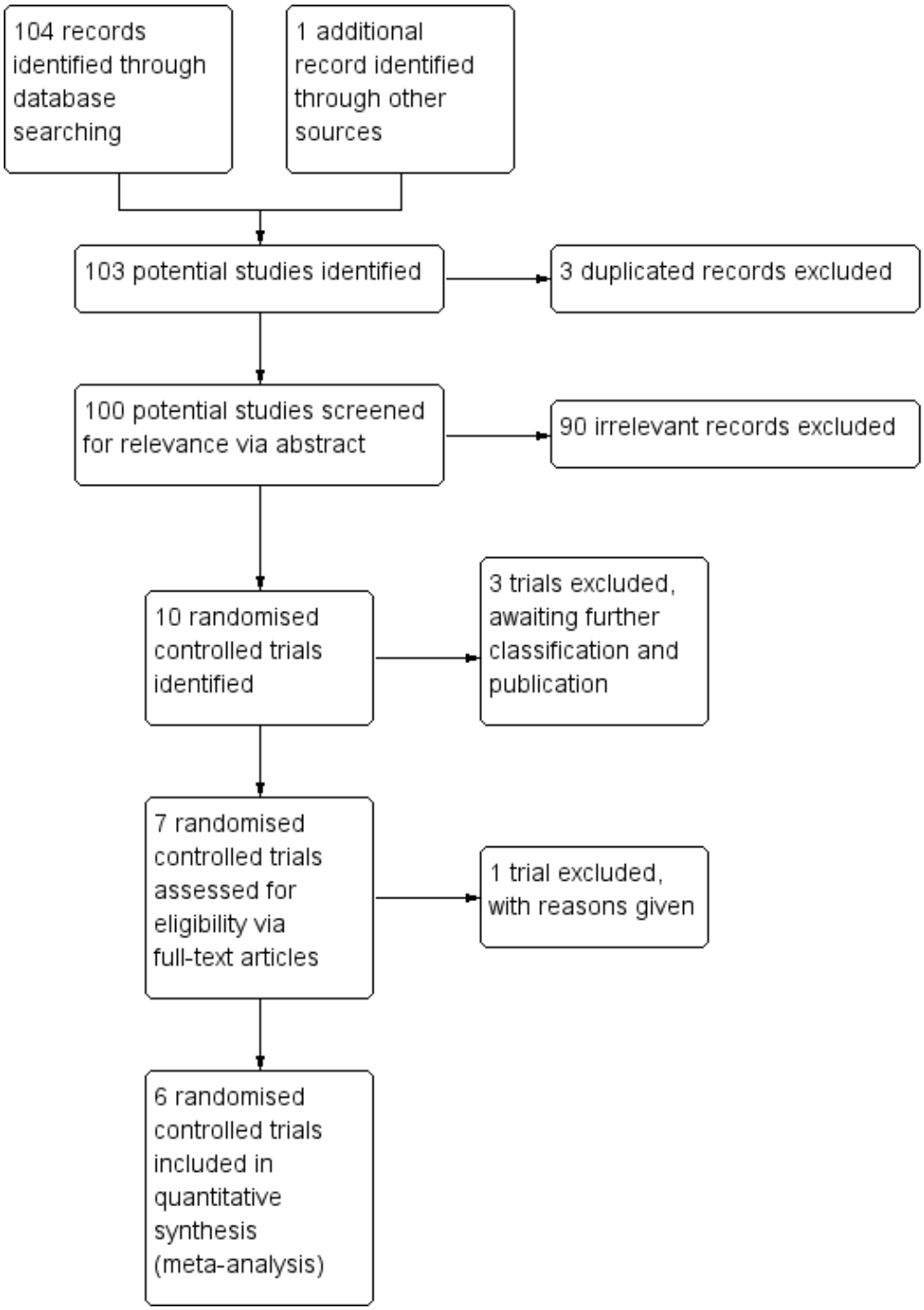
RESULTS

Description of studies

Results of the search

We obtained 105 records from our searches as described in Search methods for identification of studies. From the search result, we identified 10 randomised controlled trials (RCTs) which provided data pertinent to the non-typeable *H. influenzae* oral vaccine in preventing acute exacerbations in chronic bronchitis and COPD (Figure 1).

Figure 1. Inclusion of trials flow diagram



Included studies

We included six studies in this review (Clancy 1985; Clancy 1990; Clancy 2013; Lehmann 1991; Tandon 1991; Tandon 2010). The main features of the included trials are summarised in the Characteristics of included studies table. The methods are described here in greater detail, largely using direct excerpts of the original papers as these demonstrate the trials' strengths and weaknesses in the words of the original authors.

Overview

All six of the included studies were clinical placebo-controlled RCTs, five of which were double-blinded (Clancy 1985; Clancy 2013; Lehmann 1991; Tandon 1991; Tandon 2010) and one was single-blinded (Clancy 1990). They were conducted to test the efficacy of enteric-coated, killed preparations of *H. influenzae* in populations prone to recurrent acute exacerbations of chronic bronchitis or COPD. The vaccine preparation and immunisation regime used in all trials consisted of at least three courses of formalin-killed *H. influenzae* in enteric-coated tablets taken at intervals (for example, on days 0, 28 and 56). Each course generally consisted of two tablets taken after breakfast over three consecutive days. In all cases, the placebo groups took enteric-coated tablets containing glucose.

The trials varied in duration from three to 12 months. Randomisation in the trials was achieved by having a pharmacist independently preparing treatment packages that contained either active or placebo tablets (Clancy 1990; Lehmann 1991; Tandon 1991). These packages were numbered and randomised before being distributed to the clinicians involved in the trials, where the pharmacist was responsible for disclosing the randomised codes at the conclusion of the trial.

The trials varied in population groups, with most trials including chronic bronchitis or COPD patients in Australia with mean ages between 40 and 80 years (Clancy 1985; Clancy 1990; Clancy 2013; Tandon 1991; Tandon 2010). Lehmann 1991 was conducted in chronic bronchitis or COPD patients in Papua New Guinea, with a mean age of 51 years.

Bacterial load was assessed by a standardised method across 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 samples, transporting material and culture methods generally followed a set protocol for adequate specimen handling and control. However, the lack of consistency and wide variety of measurement styles used amongst the studies to calculate and report carriage levels made analyses between studies difficult.

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 respiratory medicine clinical criteria at the time of the respective trials. Such criteria included increase in volume and purulence of sputum, usually with increased breathlessness and sometimes fever.

Clancy 1985 was carried out and published by Clancy in 1985 and 1987 and is the oldest trial relevant to this review. It is a double-blind, placebo-controlled RCT conducted in New South Wales (Australia) over a period of three months in the winter of 1983. The mean age in the treatment group was 65.5 years and in the placebo group it was 64.7 years. Its focus was the immunogenicity of the *H. influenzae* oral vaccine and the clinical impact on patients with airways damaged by COPD who suffer recurrent episodes of acute bronchitis. Fifty patients with COPD (not taking corticosteroids or immunosuppressants) were recruited from the chest clinic of the Royal Newcastle Hospital and were given a three-day course of tablets (two daily) at 0, 28 and 56 days. Placebo and non-typeable *Haemophilus influenzae* (NTHi) vaccine were both enteric-coated. Clancy 1985 utilised two placebo arms in their trial; the first group was given enteric-coated glucose tablets and the second was given sodium tauroglycocholate. We have used the results from the first placebo group as this is a standard, widely used placebo, rather than the sodium tauroglycocholate group as this placebo may have contributed some therapeutic effect. Participants were assessed by a chest physician, lung function (spirometry), throat cultures and saliva samples collected at baseline, 28, 56 and 84 days. The characteristics of participants entered into the trial demonstrated a very representative population; older adults (mean age 65 years), majority male (M:F 4.5: 1), majority smokers (86%). *H. influenzae* was isolated from 69% of sputum samples collected during acute bronchitis episodes in this population. Clancy 1985 concluded that the NTHi vaccine resulted in over 90% protection against acute exacerbations compared to the placebo group. This was not still the case at follow-up a year later, at which point there was also no significant reduction in incidence of *H. influenzae* carriage. That is, no clear correlation between clinical protection from acute exacerbations and either carriage of *H. influenzae* or the level of antibody to *H. influenzae* antigen in saliva was evident. It was also noted that the protection provided by the vaccine did not extend to the subsequent winter, which is consistent with the knowledge that mucosal immunity is less durable than systemic immunity.

Clancy 1990 was a double-blind RCT trial conducted in Australia over a six-month period. There were a total of 37 participants with

each group having similar baseline characteristics. This study had a population with a mean age of 65.5 +/- 2.9 and they were recruited from a chest clinic in Newcastle. Episodes were defined by an increase in purulence and volume of sputum with associated fever, cough, shortness of breath and antibiotic therapy. Each participant was assessed by a chest physician, completed a respiratory questionnaire (ATS OLD 78), and had sputum and mixed saliva samples taken and lung function via spirometry. Each group received three courses of oral tablets for the three consecutive days at 0, 28, 56 days. One group received the active preparation containing *H. influenzae* vaccine while the other group received a glucose-containing placebo preparation. There was a significant reduction in the number of episodes of acute wheezy bronchitis in the treated group with a P value of 0.02. There was a significant reduction (41%) in the total number of acute infections in the treatment group compared to placebo group but no significant change when acute infections were considered in an individual from either group. This study had other modes of measuring severity, such as the number of participants reporting infections and the number of infections prescribed antibiotics, and all the results supported the treatment group. There was no significant difference noted in the side effect profile in either group.

Clancy 2013 was a double-blind, placebo-controlled, prospective study conducted for nine months over the Australian winter of 2011. Participants included 320 moderate-severe COPD participants with FEV_1 < 60%, requiring oral systemic corticosteroid therapy or admission into hospital and they were recruited from 21 sites across Australia; the mean age of participants in the treatment arm was 71.2 years and in the placebo arm was 67.9 years. Patients in the intervention group were given two HI-164 oral vaccine enteric-coated tablets per day that each contained 45 mg of the formalin-inactivated NTHi (HI-164) active vaccine, with the placebo group receiving a glucose substitute. Its outcomes assessed the number of exacerbations (according to the St George's Respiratory Questionnaire), carriage levels (from cultured sputum samples), hospitalisations and antibiotic/steroid prescriptions (based on medical records). The aim of this study was to extend the database from earlier and smaller studies showing that maximum protection occurred in those with most severe disease, with the most sensitive indicator being a reduction in exacerbations requiring corticosteroid therapy and/or hospital admission. This current study provides evidence that the age-related vaccine benefits in COPD noted with parenteral vaccines apply also to oral vaccines that enhance mucosal immunity within the bronchus. The results were only minutely significant in circumstances of low exposure to NTHi and only amongst a subgroup of younger participants (aged under 65), given more responsive immune systems and less established airway disease. The results were otherwise not significant for those older than 65 years of age.

Lehmann 1991 was a prospective, double-blind RCT, conducted through the Pneumonia Research Programme in Papua New Guinea. As a result, the demographic characteristics are significantly different to those found in high-income communities. Potential participants were identified by nomination from town residents and villagers and were then followed up by a standard questionnaire, which identified people suffering from chronic lung disease. Participants who matched the eligibility criteria were examined with lung function tests and spirometry at time of entry into the trial. Randomisation and blinding of medication and placebo was done by the pharmacy department at the Royal Newcastle Hospital, New South Wales; the placebo and active vaccine looked identical and the randomisation code was held by Auspharm International Ltd until the completion of the trial. Both groups were similar at baseline following allocation. Administration of medication was overseen by doctors and nurses to maintain compliance in the 12-month follow-up period. Patients lost to follow-up included eight in the vaccine group and three in the placebo group, with three deaths in the vaccine group and one death in the placebo group. The trial does not mention any intention-to-treat (ITT) analysis for these patients, rather stating "permanent exit from the study were excluded from the calculation", potentially creating attrition bias. The trial concludes that for the population of the highlands of Papua New Guinea the vaccine protected against episodes of acute bronchitis, but not against more severe forms of acute lower respiratory tract infection. A limitation of the study was the need for a larger population group to ensure greater statistical power to help determine the extent of protection oral *H. influenzae* vaccine could provide.

Tandon 1991 was a double-blinded RCT, conducted in 1988 at the repatriation hospital in Western Australia. This study recruited 64 participants with chronic bronchitis and a history of recurrent respiratory tract infections in order to find out whether oral NTHi immunisation is effective in this participant group. Participants were divided randomly into placebo (mean age 71.1 years) and vaccine (mean age 73.1 years) groups. All the participants followed the same treatment regime consisting of three courses of the tablets on days 0, 28 and 56. Study outcomes were acute infective episodes, number of antibiotic prescriptions and colonisation with *H. influenzae*, monitored through the following strategies: primary care physician for diagnosing acute infective episodes, sputum sample, visual analogue scale (VAS). For all of these variables, better outcomes were demonstrated in the vaccine group. Previous studies have demonstrated that *H. influenzae* was the main constituent in bacterial colonisation of the bronchus and therefore vaccinating against it would reduce the incidence of acute exacerbations, which is consistent with the results of this study.

Tandon 2010 was a multicentre, double-blind, placebo-controlled trial conducted at four sites around Australia. The study tested the efficacy of HI-164OV in reducing the number and severity of acute exacerbations in participants with severe COPD. Acute exacerbations were defined by an increase in volume and purulence of sputum. Each participant took the same regime (two tablets daily for three consecutive days) with courses repeated at day 28 and 56. All tablets were identical-looking, enteric-coated capsules that

contained either vaccine (N = 18) or placebo (N = 20). Participants were followed up every four weeks via a respiratory questionnaire, sputum and nasopharyngeal swabs were collected to monitor bacterial colonisation and blood samples were collected to monitor antibodies. The primary variables were the number and duration of exacerbations and the number of antibiotic courses prescribed. Baseline demographic characteristics, such as mean age (vaccine 69.5, placebo 67.5) were very similar, demonstrating effective randomisation. However the exact method of randomisation was not disclosed. Four of the six authors of this study disclosed that they had received funding from Hunter Immunology Limited. The authors concluded that the vaccine was safe and had a significant efficacy in participants with severe COPD. Benefits were noted with respect to a reduction in the severity of episodes (duration of episodes; 14.3 vaccine group and 22.7 placebo, P value < 0.01), which required less antibiotic therapy (event rate; 0.83 vaccine and 1.15 placebo, P value < 0.05) and fewer admissions to hospital (three in the vaccine group compared to 12 in the placebo group, P value < 0.05). However, a reduction in the incidence of episodes did not reach significance possibly because the study was significantly underpowered.

Excluded studies

We excluded one study because it did not meet our inclusion criteria (Clancy 2010). As noted in Characteristics of excluded studies, the participant population included smokers who did not have formally diagnosed COPD or chronic bronchitis and outcome measures were limited to physiological markers that did not include the clinical outcomes defined in this review's protocol.

Three studies are cited only in trial registries and pending formal publication of the raw trial data by the investigators (ACTRN12606000074594 2013; ACTRN12606000076572 2013; ACTRN12610000916044 2013). The main features of these unpublished trials can be found in Characteristics of studies awaiting classification. These trials have potential to be incorporated into future updates of this review.

Risk of bias in included studies

A summary of the 'Risk of bias' assessment is detailed in the Characteristics of included studies table.

Allocation

The random sequence generation in the studies was generally determined to be poor, with 50% of the studies graded as either high or unclear risk (Clancy 1985; Clancy 2013; Tandon 2010), because they did not provide any information regarding the random sequence generation and subsequent allocation process. We considered the remaining studies to have a low risk of bias given that there were reports that a third party conducted randomisation and the allocation codes were kept confidential until the end of the trial (Clancy 1990; Lehmann 1991; Tandon 1991).

The allocation concealment in the selected studies was generally poor, with 67% of the studies categorised as either unclear or high risk of bias (Clancy 1985; Clancy 1990; Clancy 2013; Tandon 2010). Only two studies demonstrated a low risk of bias, where the handling and distribution of the treatment packages was carried out independently by the pharmacist who employed an appropriate randomisation chart and safely kept the package trial code associated with the patient (Lehmann 1991; Tandon 1991).

Blinding

Suitable blinding was performed in all studies, except for one, which we deemed to be at high risk as it did not blind the commercially available polybacterial tablets (Clancy 1990). For this reason, the study was subsequently conducted as a single-blinded trial (participants blinded). All of the studies reported using identical enteric-coated tablets for both intervention and placebo arms of the trial.

Incomplete outcome data

Five of the six included studies accounted for and provided sufficient information regarding the follow-up of patients that dropped out of the trials (Clancy 1985; Clancy 1990; Clancy 2013; Tandon 1991; Tandon 2010). Lehmann 1991 made no mention of intention-to-treat analysis and reported a substantial loss to follow-up (eight participants from the vaccine group and three from the placebo group), especially considering the small group size.

Selective reporting

We found no selective reporting in any of the studies.

Other potential sources of bias

We identified no other potential sources of bias.

Effects of interventions

See: **Summary of findings for the main comparison**

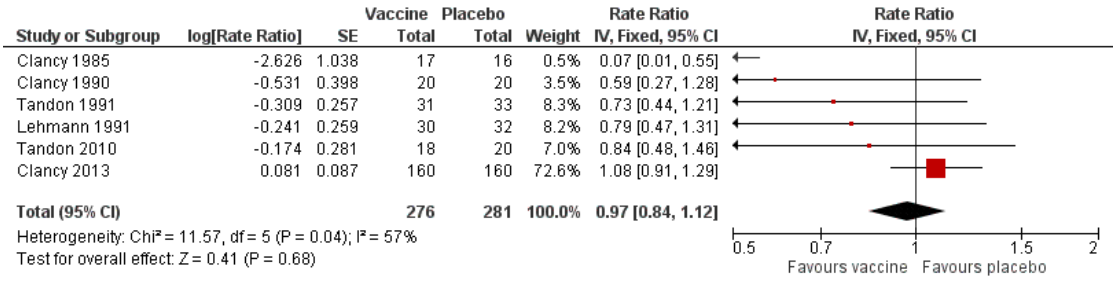
Primary outcomes

1. Incidence of acute exacerbations of chronic bronchitis or chronic obstructive pulmonary disease (COPD)

Six trials evaluating 557 patients assessed the effectiveness of nontypeable *Haemophilus influenzae* (NTHi) oral vaccination on the frequency of acute exacerbations in patients with advanced lung

disease (Figure 2; Table 1). The meta-analysis concluded that there was a small, non-significant 2.048% decrease in exacerbations in the vaccinated group when compared to the placebo group (risk ratio (RR) 0.97, 95% confidence interval (CI) 0.84 to 1.12, P value = 0.68) (Analysis 1.1).

Figure 2. Forest plot of comparison: 1 Primary outcomes, outcome: 1.1 Exacerbations (number of exacerbations/person/year).Refer to for Overall rate estimates of acute exacerbations across included studies.



Despite all trials having almost identical primary objectives, there was a considerable discrepancy in the manner in which the primary outcomes were reported. For example, Clancy 1985 reported overall number of infections, whereas Tandon 2010 reported the number of infections per participant. In order to allow meaningful comparisons between studies we converted all data into a rate of exacerbations (number of exacerbations per participant per year). Of the six studies incorporated into the review only one demonstrated an effect that favoured the vaccination group (Clancy 1985). Clancy 1985 is a small trial, which enrolled 33 participants. The data showed a very significant positive effect in favour of the vaccine group, only recording one event compared to the 13 in the placebo group, which was statistically significant (RR 0.07, 95% CI 0.01 to 0.55) despite the very large CI. However, subgroup analysis demonstrated that removing this study from the pool had no bearing on the overall meta-analysis outcome as its small population meant this study's weighting was very small.

Five studies, with a total of 504 participants, did not show a significant increase in the number of exacerbations (Clancy 1990; Clancy 2013; Lehmann 1991; Tandon 1991; Tandon 2010). As a result, their combined contribution to this meta-analysis weighting was 99.5%.

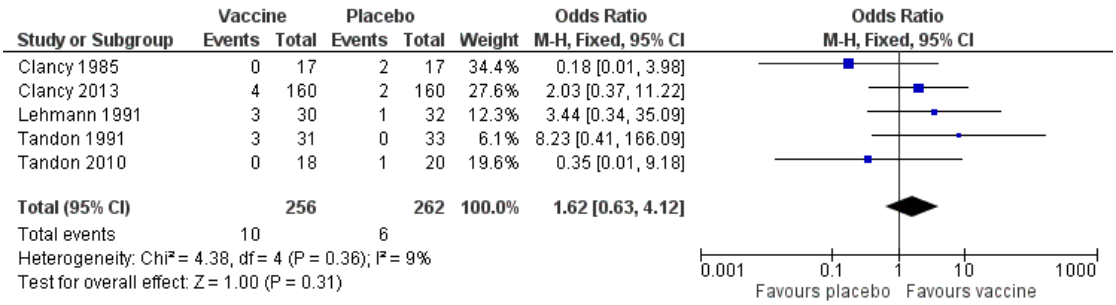
Clancy 2013 is the largest trial, comprising 320 patients and receiving over 70% of the meta-analysis weighting. It shows a non-significant 8% increase in the number of exacerbations in the placebo group (RR 1.08, 95% CI 0.91 to 1.29). Clancy 2013 reports 249 events in the vaccine group compared with 270 in the placebo group.

There is a moderate degree of heterogeneity in this meta-analysis (I^2 statistic = 57%, P value = 0.04). The study that contributes most to this effect is the Clancy 1985 trial. Removal of Clancy 1985 dramatically reduces the heterogeneity (I^2 statistic = 24% and the P value = 0.26).

2. Mortality

Mortality was not formally assessed as an outcome in any of the trials. However, five trials reported deaths of trial participants (Clancy 1985; Clancy 2013; Lehmann 1991; Tandon 1991; Tandon 2010) (Figure 3). Of these deaths, none were attributed to the vaccine and most were considered the natural endpoint of their respiratory disease or other unrelated chronic disease. There was a greater incidence of mortality in the placebo group. However, this result was not statistically significant (odds ratio (OR) 1.62, P value = 0.31), with a low amount of heterogeneity between results (I^2 statistic = 9%, P value = 0.36) (Analysis 1.2).

Figure 3. Forest plot of comparison: 1 Primary outcomes, outcome: 1.2 Mortality (deaths during trial period).



Secondary outcomes

1. Carriage level of NTHi in the respiratory tract

Analysis of carriage levels of *H. influenzae* in patients with chronic bronchitis was attempted in all six RCTs. No meta-analysis could be performed as there were a myriad of different techniques used to measure carriage levels objectively (throat swabs, sputum samples and culture) and carriage rates were measured at different intervals. Of all the trials, three failed to find a significant difference between carriage levels (Clancy 1985; Clancy 1990; Tandon 1991). Two studies showed a significant decrease in carriage rates in the vaccine group (Lehmann 1991; Tandon 2010). In one study carriage levels were measured but sputum samples could only be obtained at 36% of planned visits, of which 11% grew a respiratory pathogen; these numbers were too small to determine any significant effect following vaccination (Clancy 2013).

Lehmann 1991 showed that during acute exacerbations the mean concentrations of *H. influenzae* carriage levels were higher in the vaccine group (8.91 x 10^6 colony-forming units (cfu)) when compared against the placebo (1.55 x 10^6 cfu). However, this only equated to a 5% difference between the vaccinated and placebo arms when counting individual specimens, whereby 91% of the vaccinated and 86% of the placebo collected specimens successfully grew *H. influenzae* colonisations during the trial period.

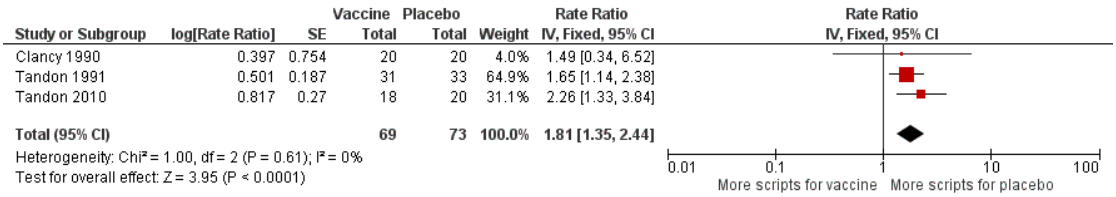
Tandon 2010 demonstrated that there was a significant (P value < 0.05) two-fold difference between the placebo and active arms in overall positive cultures (65 positive cultures in the placebo group compared to 33 in the vaccine group). However, the percentage of validated sputum samples was 50% and 48% for placebo and active groups, respectively. *H. influenzae* only accounted for 51% and 33% of positive cultures in the placebo group and the vaccinated group, respectively.

There was a trend for studies to report a transient decline in *H. influenzae* carriage levels. However, this had always returned to baseline by the end of the study time frame. Tandon 1991 noted a transient drop in carriage levels to 12% at 14 weeks in the active group, which then reverted back to 25% at 24 weeks. This is a 4% drop over 24 weeks. The placebo group noted a small 2% drop over the 24-week study period. Furthermore, in Clancy 1985 *H. influenzae* was isolated from throat swabs from 70% of the placebo group compared with 53% of the vaccination group at the end of a four-week period. Carriage rates at 12 weeks declined to 50% in the placebo group and 23% in the vaccine group.

2. Numbers of prescriptions for antibiotics and corticosteroids in the trial and follow-up periods (including hospital admissions) as an indication of severity of acute exacerbations

Four studies, evaluating 462 patients, assessed the effect of NTHi oral vaccination on the number of antibiotic prescriptions in patients with chronic bronchitis (Clancy 1990; Clancy 2013; Tandon 1991; Tandon 2010) (Figure 4; Table 2).

Figure 4. Forest plot of comparison: 2 Secondary outcomes, outcome: 2.1 Prescriptions (number of courses/person/year).Refer to for Overall rate estimates of antibiotic prescriptions across included studies.



There were considerable discrepancies amongst studies in the way antibiotic prescriptions were objectively measured. We attempted to convert the reported data into a rate (number of courses/person/year) so an objective comparison could be achieved. However, this was not possible with data from the Clancy 2013 trial, which only reported mean antibiotic use in days unlike the other studies. As a result, only three studies could be pooled in meta-analysis. Two studies did not report any information on antibiotic usage in this population (Clancy 1985; Lehmann 1991).

The three studies in the meta-analysis included 143 patients (Clancy 1990; Tandon 1991; Tandon 2010). Two of these studies produced data that favoured the vaccination group (Tandon 1991; Tandon 2010), whereas the Clancy 1990 data did not reach significance. The overall effect was a statistically non-significant 81% increase in use of antibiotic courses per person in the placebo group when compared against the vaccinated group (RR 1.81, 95% CI 1.35 to 2.44, P value = 0.61; with a RR > 1.0 indicating greater use of antibiotic usage in the placebo group) (Analysis 2.1). The majority of the weighting could be attributed to Tandon 1991 and Tandon 2010; 64.9% and 31.1%, respectively, and both favoured the vaccination group.

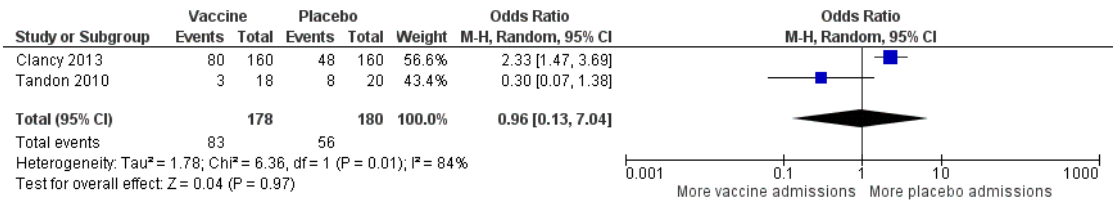
Tandon 1991 showed a significant decrease in antibiotic prescriptions (45 in the active group and 79 in the placebo group). Tandon 2010 showed a significant 56% reduction in the number of prescribed antibiotics following active treatment (P value < 0.05). The Clancy 1990 trial reports a reduction in the number of antibiotics in the active group compared to placebo, but this failed to reach statistical significance.

The Clancy 2013 trial is by far the largest study in this review (three times the combined size of the other three trials), contributing 320 of the 462 patients. Clancy reported that there was no significant difference between the two groups in terms of antibiotic usage (active group 13.5 days per episode with a range of 0 to 289; placebo group 14 days per episode with a range of 1 to 122). Given the wide and varied protocols for antibiotic administration it was impossible to translate this into course/person/year as with the other trials.

Corticosteroid prescriptions were not strictly studied as an outcome in the studies, and thus we did not meta-analyse these; nonetheless, usage was noted in participants in at least two studies (Clancy 2013; Tandon 2010), and we have considered their indications and study findings for their use in the Summary of main results.

Hospitalisation data amongst the studies were limited, with only two studies reporting hospitalisations of their participants (Clancy 2013; Tandon 2010), with significant heterogeneity noted (I^2 > 84%). The results demonstrate no significantly increased likelihood of being hospitalised in either the vaccinated or placebo group (OR 0.96, 95% CI 0.13 to 7.04, P value = 0.97) (Analysis 2.2; Figure 5).

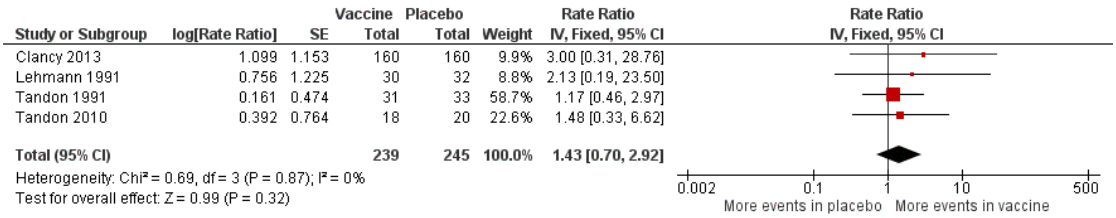
Figure 5. Forest plot of comparison: 2 Secondary Outcomes, outcome: 2.2 Hospital admissions (number of patients hospitalised during trial period).



3. Any associated adverse side effects from the NTHi vaccination, measurable from symptomology and participant reports

All studies, except Clancy 1985, reported adverse events, although none of the trials studied this as an outcome. In total, between the other studies, 142 adverse events were reported; of these, 72 occurred in the active group and 68 occurred in the placebo group (Analysis 2.3; Figure 6; Table 3). Reported adverse effects were largely gastrointestinal in nature, although others commonly reported increased dyspnoea or general malaise; none of these were directly evidenced to be attributable to the oral vaccine.

Figure 6. Forest plot of comparison: 2 Secondary outcomes, outcome: 2.3 Adverse events (number of adverse events/person/year).Refer to for Overall rate estimates of adverse events across included studies.



Clancy 2013 reported that adverse event rates were similar in both groups (placebo group 33.5% compared with 38.5% in the vaccinated group), although the actual number of events was not provided in the original publication. Further data additionally requested from the study authors show that one participant in the active group had an adverse event compared with three in the placebo group.

4. Quality of life

Only two studies reported quality of life measurements, however they used different assessment scales and are not comparable; we therefore did not meta-analyse them (Clancy 2013; Tandon 1991). Tandon 1991 reported a global assessment for general well-being using a visual analogue scale (VAS). It reports at 24 weeks a median score of 5.0 in the vaccine group compared to 2.5 in the placebo group (P value = 0.09). Clancy 2013 measured quality of life using the St George's Respiratory Questionnaire for COPD (SGRQ-C) for those under 65 years old. They reported a significant difference in symptom scores in favour of the vaccine group at three months (P value = 0.02) and six months (P value = 0.01). Data were not provided for older age groups.

DISCUSSION

Summary of main results

Incidence of acute exacerbations of chronic bronchitis or chronic obstructive pulmonary disease (COPD)

In this review we evaluated the effectiveness of a non-typeable *Haemophilus influenzae* (NTHi) oral vaccination in reducing acute exacerbations in patients with chronic bronchitis/chronic obstructive pulmonary disease (COPD). The results indicate that the vaccination has no significant impact in reducing the number of exacerbations. Only one study was able to demonstrate a statistically significant effect, which favoured vaccination (Clancy 1985). This was the smallest study and contributed significant heterogeneity to the meta-analysis. When we removed Clancy 1985 from the meta-analysis, we found no significant difference for the primary outcome. All other studies showed no significant treatment effect. Among the studies included in the review, there are considerable differences in the methodology and intervals at which measurements were recorded. The main outcome (acute exacerbations) was measured differently across the six studies, providing a challenge for comparison. For example, Clancy 1985 records results as

a proportion whereas Lehmann 1991 utilises rates. There are also notable discrepancies in the study time periods, with Clancy 1985 reporting data at three months and Clancy 1990 providing data up to six months. Data recorded at nine to 12 months could only be elicited from two trials. As a result we converted all data into rates so that studies could be objectively compared, irrespective of their varying follow-up protocols.

Other differences amongst the trials included variation in population (Lehmann 1991 was conducted in Papua New Guinea), the use of subjective measurements such as respiratory questionnaires to measure exacerbations and seasonal variations. These may have contributed to the marked heterogeneity (I^2 statistic = 57%; P value = 0.04) identified in the meta-analysis.

Only one study was large enough to be able to conduct subgroup analysis stratified by age (Clancy 2013). A subgroup analysis excluding all patients greater than 65 years of age concluded that the mean number of exacerbations was significantly higher in the placebo group (56) when compared to the vaccinated group (34) (P value = 0.0015). There was also a statistically significant difference in the days to first exacerbation (87 days in the placebo group compared to 111 days in the vaccine group). Although the data are limited at this stage, these results suggest the use of the NTHi vaccination in a younger population, especially considering that there was no difference in mortality or adverse events in these two groups. The apparently greater efficacy of the vaccine seen in those less than 65 years old may be a reflection of a less severe burden of disease; younger patients generally have a shorter smoking history, fewer exacerbations and fewer co-morbidities. Further studies need to be conducted in younger patients and considering the varying severity of COPD to identify whether there is a significant treatment effect in this population.

Mortality

We found mortality rates overall to be higher in the placebo group. However, these results were not statistically significant and are unconvincing. There was no apparent association with treatment effect and it is unclear whether the administration of the NTHi vaccine contributed to mortality.

Other patient factors were suggested in some trials to contribute to mortality, such as long-standing cirrhosis or a ruptured aneurysm reported in Tandon 1991 and Lehmann 1991. These co-morbidities would have a significant effect on the mortality outcome given the small participant numbers.

Two trials reported the primary cause of death as a terminal respiratory infection (Lehmann 1991; Tandon 1991), with other studies reporting cause of death to be non-respiratory. Whilst it is understood that the most common cause of death in COPD patients is respiratory failure, it was not clearly demonstrated in this meta-analyses, which was likely due to inconsistent and insufficient reporting in the studies.

Carriage level of NTHi in the respiratory tract

All six trials measured sputum carriage levels of *H. influenzae*; these were obtained routinely and during acute exacerbations, although the methods of reporting and intervals at which routine samples were taken differed. This limited the extent to which these results could be compared.

A significant difference in the carriage rates was not consistently found between the placebo and vaccine groups in every trial. No significant difference over time in routine carriage rates was found between the groups in Clancy 1985, Lehmann 1991 and Tandon 1991. The largest of the studies obtained samples at only 36% of visits and of these, a respiratory pathogen was isolated in only 11% (Clancy 2013). The sputum carriage levels were too small to determine any significant effect following vaccination.

In the majority of trials, *H. influenzae* was noted to play a prominent role during infective exacerbations. In Clancy 1985, *H. influenzae* was isolated from 69% of sputum samples collected during acute exacerbations; and from 33% and 44% in the placebo and vaccine groups respectively in Clancy 1990 (this difference was not significant). Lehmann 1991 and Tandon 2010 did not discuss the bacterial carriage specifically during acute exacerbations. It is notable that Tandon 1991 found that the numbers of acute infective exacerbations were higher (P value = 0.011) in participants in the vaccine group from whose sputum *H. influenzae* was isolated either before or during an acute episode.

Clancy 2013 noted that of the sputum samples that grew a respiratory pathogen, *H. influenzae* played a role, but not a prominent one, accounting for only 6%. 6.2% grew *Streptococcus pneumoniae*, 7.5% *Moraxella catarrhalis* and 6.0% *Pseudomonas aeruginosa*. Clancy 1990 noted that during the six-month trial, the proportion of *H. parainfluenzae* infections was between 57% and 89% greater than the proportion of *H. influenzae* infections during the same time period across both groups. This poses the question of the clinical impact of treating *H. influenzae* as prophylaxis, as the background carriage rates may reflect the rates in acute exacerbation. Also, many of the studies did not mention whether other pathogens were also found in the sputum samples that isolated *H. influenzae*; how many acute exacerbations are due to multiple organisms?

The population studied in the Papua New Guinea study (Lehmann 1991) raises concerns about the potential applicability of the results to the COPD patient in a high-income country. Asymptomatic background carriage rates were high; 57% of routine sputum samples isolated *H. influenzae* (37% isolated *S. pneumoniae* and 11% demonstrated *H. parainfluenzae*). There were also some significant methodological problems, with 53 out of 362 samples having to be excluded due to betel nut consumption or epithelial contamination.

Numbers of prescriptions for antibiotics and corticosteroids in the trial

Antibiotics were prescribed in four out of the six clinical trials (Clancy 1990; Clancy 2013; Tandon 1991; Tandon 2010), but this was not necessarily an effective outcome measure that correlated with disease progression or severity. Given the high variability and lack of consistency concerning antibiotic course administration and measurements, a truly uniform assessment and comparison could not be performed amongst the trials. Whilst the three studies pooled for quantitative analysis appear to indicate slightly more prescriptions having been issued to participants in the placebo group (odds ratio (OR) 1.81, P value < 0.05) (Clancy 1990; Tandon 1991; Tandon 2010), this conclusion remains unconvincing. There was also no reported follow-up regarding what effect antibiotics had on patients (that is, for instance, if there was resolution of symptoms or reduction in carriage levels).

The application of current therapeutic guidelines in the trials was similarly questionable, with the intentions and protocols for prescribing antibiotics largely unclear and not reported in their methods. It is understood that at least half of patients with chronic bronchitis and COPD are persistently colonised with *H. influenzae*, *S. pneumonia* or *M. catarrhalis* (Lehmann 1991), hence a positive sputum culture that is not necessarily indicative of an acute infection and subsequent antibiotic prescription (in Tandon 2010, 48% in the vaccinated group and 50% in the placebo group had a validated positive sputum culture). Normally in exacerbations of COPD, sputum cultures would only be done if there was a failure of response to treatment or if the patient had repeated bacterial exacerbations within several months. Nonetheless, these organisms may be responsible for more severe exacerbations, in which antibiotics have been shown to be of benefit. The aim of treatment with antibiotics in acute exacerbations should be to alleviate symptoms and reduce the volume of sputum rather than total elimination of colonising organisms.

None of the trials specified the class of antibiotic therapy used, nor did they explore sensitivities. This is important given that currently only amoxicillin and doxycycline regimes have been shown to be superior over other antibiotic classes, such as macrolides, which fail to suppress *H. influenzae* (Longo 2011).

Corticosteroid use was measured as an outcome in two trials (Clancy 2013; Tandon 2010). Clancy 2013 reported a median duration of five treatment days (minimum 0, maximum 313) in the vaccine group and 10 days (minimum 0, maximum 306) in the placebo group. Tandon 2010 reported a 56% reduction in the proportion with acute exacerbations with corticosteroid treatment; for all episodes the proportion with recurrent exacerbations was less than in the treated group (0.33 per participant compared with 0.55 per participant, 40% reduction).

Even though two studies reported the use of corticosteroids for the treatment of acute exacerbations, this does not preclude participants from receiving corticosteroids prior to and during the studies. Many of the participants were admitted to hospital during the study period and were likely to have received a short course of systemic corticosteroids (in Clancy 2013 and Tandon 2010, a total of 83 participants in the vaccinated groups and 56 in the placebo groups). Short (not extended) courses of oral prednis(ol)one or intravenous hydrocortisone have been shown to shorten the duration of hospital admission and hasten return to previous lung function and stable symptom control and are routinely used for severe exacerbations of COPD (Longo 2011).

Hospitalisations

Two studies reported hospitalisations (Clancy 2013; Tandon 2010). There are limited data and information in the studies regarding participant hospitalisations; Analysis 2.2 demonstrates that those vaccinated were no more unlikely to be hospitalised (OR 0.96, 95% confidence interval (CI) 0.13 to 7.04, P value = 0.01) based on a simple count of the number of participants having been hospitalised during the respective study period. Further data parameters, such as length of hospital stay and intensive care versus general ward admission, would have been necessary for a more complete analysis.

In the Tandon 2010 study, admissions to hospital were very high in the placebo group, with 11 admissions compared to one admission in the vaccination group. This demonstrates that those receiving the NTHi vaccine had the chance of hospital admission reduced by 90% (P value = 0.05). A similar outcome was noted in Clancy 2013, showing a 50% reduction in hospital admissions following an acute exacerbation in the vaccine group (P value = 0.047).

Any associated adverse side effects from the NTHi vaccination, measurable from symptomology and participant reports

There was no clear definition of what constituted an adverse effect and therefore no consistency between the studies' reporting of adverse events. For example, Tandon 1991 includes increase of dyspnoea and cough as an adverse event, while Clancy 2013 reports mortality as a severe adverse event. Methods used for monitoring adverse events were not reported in any of the trials. Thus there is potentially an under-reporting of less severe side effects. No clear comparisons or conclusions could be reached regarding any association between adverse effects and therapeutic effect. The adverse effects presented in the trials may well have been attributable to the significant comorbidity of the patient rather than to the vaccine. To discern whether these symptoms or adverse effects were true side effects of the vaccine or whether they were sequelae of the patient's disease process was not possible in this review as insufficient primary study data were available.

Quality of life

Only two studies reported quality of life (QoL) measures (Clancy 2013; Tandon 1991), and these trials used different measurement

tools, limiting comparisons that could be made between the results. It is also notable that, by nature, the measurement of quality of life is subjective and difficult to quantify; neither studies provided further data and information regarding which aspect of QoL was most improved. Nonetheless, both trials report at least a two-point improvement in patient QoL in the vaccinated groups versus placebo. Improvement in QoL was based on overall clinical condition assessed at the start of the trial and at set points during the trial. These intervals were slightly different between the two trials, with Tandon 1991 measuring at six months and Clancy 2013 measuring at three and six months. Clancy 2013 did not provide data on QoL for participants over 65 years of age.

Overall completeness and applicability of evidence

Although the number and size of the studies were low, all the trials included participants with established chronic obstructive pulmonary disease (COPD) or chronic bronchitis. Clancy 2013 was the only study with sufficient sample size to conduct subgroup analyses that assessed the effects of the vaccine in patients less than 65 years of age. The majority of studies (with the exception of Lehmann 1991, which was conducted in Papua New Guinea) were conducted in an Australian population. However, trial length and follow-up periods varied from three to 12 months among the trials. The majority of the studies administered the HI-164 oral vaccine enteric-coated tablets (two per day), which each contained 45 mg active substance of formalin-inactivated NTHi, which was compared with enteric-coated placebo tablets (with the exception of Clancy 1985, which used a sodium tauroglycocholate substitute for the placebo). All studies had comparable objectives that assessed the vaccine's effect on acute COPD exacerbations.

We consider the results of this review to be applicable to patients with established COPD.

Quality of the evidence

Overall, the methodological quality of the trials was acceptable with most reporting methods of random sequence generation and allocation concealment sufficiently to assess them as adequate. The greatest limitation of the included studies is that of the six trials one is by far the largest in terms of included population. The smaller studies were underpowered and even when pooling the five smaller studies, their weighting is inferior to that of the one larger trial (Clancy 2013).

The assessment of primary outcomes of acute exacerbations was carried out through respiratory questionnaires, which are subjective, instead of using objective measures such as spirometry. Other secondary outcomes, such as *H. influenzae* colonisation and antibiotic use, are more objective measurements but may be difficult to measure. Studies had low rates of losses to follow-up and attrition rates were low and equal in both arms of the trials.

There is a moderate degree of heterogeneity to be found in this meta-analysis, specifically in the outcome that measures the number of acute exacerbations of COPD (I^2 statistic = 57%, P value = 0.04). Clancy 1985 appears to contribute most to the heterogeneity; its exclusion from the analysis dramatically reduces heterogeneity (I^2 statistic = 24% and P value = 0.26) and can likely be attributed to the study's reported result of only one exacerbation in the vaccinated group. Nonetheless, the exclusion of Clancy 1985 from the meta-analysis did not appear to have a significant impact on the overall result, given the small study size of approximately 30 patients and the robustness of the data sourced from the remaining studies.

Potential biases in the review process

Two review authors conducted all data selection and extraction independently, with a third author acting as an arbiter, in order to minimise the risk of error and bias. One of the authors (AC) was involved as an investigator in four of the six included trials (Clancy 1985; Clancy 1990; Clancy 2013; Lehmann 1991), but not involved in the data extraction and analysis in the review in order to reduce interpretation bias.

It is possible that despite extensive searching we may have missed a trial. However, this is very unlikely as one of the review authors is a world-renowned expert in the field and has consulted his extensive network to search for additional unpublished data. Therefore, we think that we have captured all available evidence in this review.

Agreements and disagreements with other studies or reviews

This is an update of a previously withdrawn Cochrane review of the same title (Foxwell 2006). The authors of the previous review concluded that the vaccine was efficacious in reducing 20% to 30% of acute exacerbations in COPD patients and supported its use clinically. They also concluded that there was a need for larger clinical trials to assess longer-term prognosis. Since publication of the previous review a new trial with a substantially larger population has been published (Clancy 2013), and we have been able to include this in our updated meta-analysis. As a result of the inclusion of this large trial the validity of the review has increased and the conclusions have changed substantially.

AUTHORS' CONCLUSIONS

Implications for practice

This review analysed six trials of monobacterial whole, killed, non-typeable *H. influenzae* (NTHi) vaccine in patients experiencing recurrent acute exacerbations of chronic obstructive pulmonary disease (COPD). Our results do not support the use of the vaccine in reducing the number and severity of exacerbations.

Implications for research

Future trials should address the long-term effects of the NTHi oral vaccine. It would be useful to assess further both the outcomes at 12 months and two years following the initial vaccination, alongside gathering data on mortality, age and other contributing factors. It may also be useful to assess the effect of regular (seasonal) vaccination over a longer period of time. Careful standardisation of the measurement protocols is necessary for consistent analyses for outcomes in the areas of number of acute infective exacerbations, severity of exacerbations, carriage levels of *H. influenzae* and associated microbiology, hospital admissions and prescription of antibiotics and corticosteroids. As polymerase chain reaction (PCR) is becoming more widely used in the diagnosis of infection, it may have a role in future research given the limitations of cultures, especially for micro-organisms such as *H. influenzae*, which are difficult to serotype. Future studies should more clearly assess and consider the use of antibiotics and steroids in COPD patients with *H. influenzae*, as these are common therapies that have a significant influence on mortality and morbidity, alongside bronchodilators, oxygen therapy and ventilatory support.

The concept that COPD is a chronic condition with a peak incidence of diagnosis in patients aged between 50 and 60 years of age means that patients involved already have well-established airway disease. Whilst the inclusion criteria for this review and trials concerning this vaccine specified those already diagnosed with COPD, it is equally important to assess the potential benefits of vaccinating patients with a pre-disposition to developing COPD (for example, younger populations of heavy smokers with mild airway disease that have not reached a chronic condition yet). Future research should therefore also be directed at assessing the effects of *H. influenzae* oral vaccination in high-risk populations not yet diagnosed with COPD, as a means of establishing the prophylactic capabilities of such a vaccine.

The projected annual cost of COPD in the United States will increase from USD 176.8 to USD 832.9 billion in the next 20 years, with the majority of direct costs attributed to acute exacerbations (Lee 2006). As COPD is a non-curable disease, any cost-effective intervention to prevent exacerbations would be worth further research, considering the rising global prevalence and financial burden of treatment on the health system.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Clancy 1985

Methods	Double-blind, placebo-controlled, prospective RCT over a 3-month winter period in 1983
Participants	50 patients from Royal Newcastle Hospital with chronic obstructive lung disease (COPD) not taking corticosteroids or immunosuppressants Mean age of all participants: 65.5
Interventions	NTHi vaccine and 2 placebo arms (enteric-coated glucose tablets or 25 mg sodium tauroglycocholate). 3 courses of tablets were taken at 0, 28, 56 days. Each course was 2 tablets taken before breakfast on 3 consecutive days
Outcomes	1. Number of lower respiratory infections 2. *H. influenzae* isolation 3. Salivary antibodies
Notes	Many participants were taking antibiotics and bronchodilator agents but were not taking steroids or immunosuppressants Ciba Griegy (Australia) was cited for financial assistance in the discussion Trial was conducted at the Royal Newcastle Hospital

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Randomisation was completed independently by a "Dr Smith" who kept the trial code allocations privately; how randomisation was performed has not been disclosed. Whilst Dr Smith is not one of the trial authors, the exact nature of their relationship with the study is unknown. Randomisation in 1 arm had a very uneven male to female ratio
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	For each participant with an acute upper and lower respiratory infection, an infection questionnaire was completed by doctors who were not involved with the study and had no knowledge of the patient's test group

Clancy 1985 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	1. Infection questionnaire with an independent doctor with no knowledge of test group 2. Sputum cultures collected to detect *H. influenzae* involvement objectively 3. Blood tests collected to assess salivary antibodies objectively
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were accounted for. 2 participants out of the 50 originally enrolled died during the study
Selective reporting (reporting bias)	Low risk	Nil
Other bias	Low risk	Nil

Clancy 1990

Methods	Single-blind RCT
Participants	6-month study on Australians recruited during winter 1986 through radio station advertisement Mean age of 47.4 in the vaccine arm and 46.3 in the placebo arm
Interventions	Oral vaccination with killed NTHi and placebo with glucose both were enteric-coated
Outcomes	1. Total number of episodes of acute bronchitis 2. Number of episodes of acute wheezy bronchitis 3. Reduction in antibiotic use
Notes	Participants assessed on admission to trial and at 3 and 6 months during the trial. Most participants had previously unrecognised smoking-related chronic lung disease. 72% smokers and 58% had chronic bronchitis. Participant admission criteria were > 3 episodes of acute bronchitis (cough productive with sputum) over previous 2 years and an absence of chronic lung disease determined at clinical interview Trial was conducted as joint research at the Royal Newcastle Hospital and Macquarie University There was no disclosure of financial assistance

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Participants coded and randomised by an independent third party into 2 groups. 40 participants were admitted to study; 37 completed the 6-month trial. Randomisation gave well-matched treatment groups, which were equal at baseline measurement.

Clancy 1990 (*Continued*)

		There was no significant reduction in the number of participants suffering from an episode of acute bronchitis
Allocation concealment (selection bias)	High risk	Participants were allocated to the intervention group based on periods of acute bronchitis that had been assessed by a nurse practitioner using an infection questionnaire, which may have room for subjectivity
Blinding of participants and personnel (performance bias) All outcomes	High risk	Medication had the same regime and administration for both groups. In the treatment arm given the active preparation each tablet contained 10 x killed NTHi. The placebo arm were given a preparation containing glucose. Both were 2 enteric-coated tablets before breakfast on each of 3 consecutive days and repeated at 28 and 56 days. However, only participants were blinded in this study (single-blinded)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	1. A questionnaire was used to diagnose acute bronchitis and the side effects of the vaccine, which may be subjective according to the marker. However, the questionnaire did include a detailed range of signs/symptoms to be supported with routine haematological, biochemical and immunological test results (including a throat swab and Gram staining to validate the sputum) 2. The differentiation of a wheeze from a normal acute bronchitis event is not clearly defined 3. Antibiotic use was measured objectively
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were accounted for. 3 participants dropped out from the study: 2 from the placebo arm, 1 from the active arm due to poor compliance
Selective reporting (reporting bias)	Low risk	Nil
Other bias	Low risk	Nil

Clancy 2013

Methods	The study was a double-blind, placebo-controlled, prospective study for 9 months over the Australian winter of 2011
Participants	320 moderate-severe COPD participants with FEV_1 < 60% predicted were recruited from 21 sites across Australia Mean age of participants in the vaccine arm was 71.2 and in the placebo arm was 67.9
Interventions	HI-164 oral vaccine enteric-coated tablets (2 per day) that each contained 45 mg active substance of formalin-inactivated NTHi (HI-164)

Outcomes	1. Number of moderate-severe exacerbations 2. Number of hospital admissions 3. Number of corticosteroids and antibiotics prescribed
Notes	This was a multi-centre trial conducted over various health districts across Australia The trial does not cite any financial acknowledgement

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Does not disclose method. Randomisation mentioned but technique not specified
Allocation concealment (selection bias)	Unclear risk	Does not disclose method. Participants assumed to be blinded to the allocation process and blinded to whether treatment or placebo received
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded study with same administration of medication for both treatment and placebo arms. The treatment consisted of 3 courses of tablets - each course was 2 tablets daily (before breakfast) for 3 consecutive days, with courses repeated at day 28 and day 56. Following randomisation, participants attended site visits at weeks 4, 8, 12 and thereafter at 4-week intervals until week 36. The placebo group had the same regime, except with matched placebo tablets
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blinded study where at all visits acute episodes and background symptoms were recorded by a questionnaire. To document change in day-to-day symptoms all patients used a diary and the St George's Respiratory Questionnaire for COPD patients (SGRQ-C) (version 1.1; 11-12008) was administered at visit 2 (baseline), visit 5 (week 12), visit 6 (week 24) and visit 7 (week 36)
Incomplete outcome data (attrition bias) All outcomes	Low risk	320 participants were the ITT population, with a 10% drop-out rate anticipated to ensure that greater than 270 completed the study as required by the power analysis. Specifically, adverse event rates were simi-

		lar in both groups: serious adverse events (placebo 33.5%; active 38.5%) with 4 deaths in the active group and 2 in the placebo group. None of these events were considered to be due to treatment modality
Selective reporting (reporting bias)	Low risk	Nil
Other bias	Low risk	Nil

Lehmann 1991

Methods	RCT of 12 months duration, double-blind, placebo-controlled
Participants	Adults identified as suffering from chronic lung disease 62 participants included Setting: PNG highlands (under study surveillance) Recruitment: nominated Inclusion: productive cough fitting the time criteria for chronic lung disease Mean age of participants in the vaccine arm was 52.6 and in the placebo arm was 53.7
Interventions	Oral inactivated vaccine containing 10 *H. influenzae* Control: placebo, not specified Duration: 2 tablets in the morning for 3 consecutive days at monthly intervals for 3 consecutive months
Outcomes	1. Incidence of acute exacerbations 2. Bacterial carriage 3. Adverse side effects of NTHi vaccine
Notes	An acute exacerbation is defined as an increase in the volume and purulence of sputum with no evidence of respiratory distress, with or without chest pain or fever. This definition was consolidated with clinical examination, respiratory questionnaire in Melasian pigeon English, spirometry and sputum samples Conducted at PNG institute of medical research. Auspharm International Ltd cited in acknowledgements for setting up study and ongoing support

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The investigators describe appropriate random sequence generation using a randomisation code for the courses of vaccine and placebo tablets
Allocation concealment (selection bias)	Low risk	Investigators enrolling participants could not foresee assignment as randomisation

Lehmann 1991 (*Continued*)

		was performed by the third party "Auspharm International Ltd." in New South Wales accounting for the concealment of allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind trial. Blinding of participants and key study personnel ensured and unlikely that the blinding could have been broken
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind trial. The outcomes assessed in both groups were measured using the same questionnaire and a medical examination. Methods of ensuring blinding of outcome assessment were not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Concluded from the trial report, there is no mention of ITT for participants lost to follow-up (8 from vaccine group and 3 from placebo group). This is substantial considering the small group sizes; it is possible that it had an effect on the outcome
Selective reporting (reporting bias)	Low risk	Study report fails to include results for a key outcome (prescription rate of antibiotics) that would be expected to have been reported for such a study, although the protocol is not available. However, all primary outcomes are reported
Other bias	Low risk	The study appears to be free of other sources of bias

Tandon 1991

Methods	6-month RCT, double-blind, placebo-controlled
Participants	Adults with history of chronic bronchitis with recurrent respiratory tract infections (RTIs) 64 patients included Mean age vaccine group: 73.1 years; placebo group: 71.1 years Settings: Chest Clinic, Western Australia Inclusion: chronic bronchitis, documented recurrent RTIs, presence of *H. influenzae* in sputum Exclusion: COAD patients without recurrent RTIs, or on long-term antibiotics
Interventions	The oral vaccine contained 10 killed *H. influenzae* Control: placebo was a lactose substitute for bacteria Duration: 2 tablets in the morning for 3 consecutive days monthly for 3 consecutive months (day 0, 28, 56)

Tandon 1991 (*Continued*)

Outcomes	1. Incidence and occurrence of acute infections 2. NTHi carriage 3. Number of courses of antibiotics prescribed 4. Adverse effects of the vaccine 5. Quality of life (VAS score)
Notes	Acute exacerbation defined as: increase in volume and purulence of sputum usually associated with an increase in breathlessness and/or fever requiring treatment with antibiotics Exacerbation assessed by the trial authors with the following: physical exam, respiratory questionnaire (ATS DLD 78), lung function via spirometry and sputum samples Auspharm cited for providing Bronchostat and placebo tablets. Conducted at the repatriation hospital Western Australia

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The investigators describe a randomisation methodology in the sequence generation process - a randomisation chart
Allocation concealment (selection bias)	Low risk	Investigators enrolling participants could not foresee assignment because pharmacy-controlled central allocation was used to conceal allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind. Blinding of participants and key study personnel ensured and unlikely that the blinding could have been broken
Blinding of outcome assessment (detection bias) All outcomes	Low risk	This study does not report the method of ensuring blinding of outcome assessors. Respiratory questionnaire was used to collect data for primary outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	10 participants lost to follow-up (3 in vaccine group and 7 in placebo group) were analysed by intention-to-treat, which showed no significant differences For dichotomous outcome data, the proportion of missing outcomes compared with the observed event risk was not enough to have a clinically relevant impact on the intervention effect estimate
Selective reporting (reporting bias)	Low risk	The published report includes all expected outcomes

Tandon 1991 (*Continued*)

Other bias	Low risk	The study appears to be free of other sources of bias

Tandon 2010

Methods	4-month double-blind, placebo-controlled RCT carried out in winter in 4 centres in Western Australia
Participants	People with severe COPD defined by FEV_1 < 50% or > 2 acute exacerbations per year for 2 consecutive years Mean age of participants in the vaccine arm was 69.5 and in the placebo arm was 67.3
Interventions	HI-1640V; each tablet contained 45 mg approximately 10 bacteria of formalin inactivated NTHi provided as enteric-coated tablets Control: enteric-coated placebo tablets containing excipients only Duration: protocol stated that participants took 3 courses of 2 tablets in the morning for 3 consecutive days with courses repeated at 28 and 56 days
Outcomes	1. Number and severity of acute episodes (increase in volume and purulence of sputum) 2. Antibiotic courses 3. Sputum bacteriology and immune markers 4. Hospitalisations 5. Adverse effects
Notes	Multicentre trial. Most authors disclosed contributions from Hunter Immunology Limited

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Participants were reportedly randomised although the method of randomisation was not discussed. Baseline characteristics suggest that randomisation was successful
Allocation concealment (selection bias)	Unclear risk	No information was provided about the procedure for protecting the randomisation process so that the treatment to be allocated was not known before the patient was entered into the study
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind trial

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary outcome was measured using a respiratory questionnaire. This subjective data are prone to recall bias. Secondary outcomes were objectively measured using bacterial colonisations and antibody titres
Incomplete outcome data (attrition bias) All outcomes	Low risk	Participants were followed up for 4 months after completing the 3 courses. No patients were lost to follow-up. Data surrounding withdrawal and discontinuation from the study were well described
Selective reporting (reporting bias)	Low risk	The published report includes all expected outcomes
Other bias	Low risk	No other sources of biases were identified

COAD: chronic obstructive airways disease
COPD: chronic obstructive pulmonary disease
FEV1: forced expiratory volume in one second
H. influenzae:*Haemophilus influenzae*
ITT: intention-to-treat
NTHi: non-typeable *Haemophilus influenzae*
PNG: Papua New Guinea
RCT: randomised controlled trial
RTI: respiratory tract infection
VAS: visual analogue scale

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

Study	Reason for exclusion
Clancy 2010	The participants and outcome measures of this study did not match this review's protocol. Participants were smokers with no clearly defined respiratory disease. Outcome measures were limited to physiological markers as opposed to the clinical outcomes of this review

Characteristics of studies awaiting assessment *[ordered by study ID]*

ACTRN12606000074594 2013

Methods	Subjects will be randomly allocated to active tablets each containing 45 mg HI-1-164-AS (inactivated non-typeable *Haemophilus influenzae*). Study medication (2 tablets) will be taken on days 1, 2, 3, 29, 30, 31, 57, 58, 59. The live phase of the study will be of 8 months duration (March to October)
Participants	Both males and females, greater than or equal to 18 years of age, with moderate to severe airway disease Total number of participants is 124; randomised to either active or placebo groups
Interventions	HI-1-164-AS (inactivated non-typeable *Haemophilus influenzae*) oral vaccine tablet
Outcomes	*Primary outcomes*: number of episodes of acute bronchitis during the study; proportion of participants experiencing an episode of acute bronchitis during the study; duration of episodes of acute bronchitis during the study; number of courses of antibiotics taken for treatment of acute episodes of bronchitis during the study *Secondary outcomes*: NTHi-specific antibody; pharyngeal colonisation with *Haemophilus influenzae* (*H. influenzae*); presence of *H. influenzae*, *M. catarrhalis*, *S. pneumoniae* and *Pseudomonas* species in sputum; severity of episodes of acute bronchitis
Notes	It was planned in this trial that the analysis of the severity of episodes of acute bronchitis was to be based on the respiratory questionnaires completed by the patients at the time of each episode. However, insufficient respiratory questionnaires were completed during the study to allow for analysis of the data collected. In accordance with recent draft guidance for industry for developing drugs for treatment of COPD issued by the FDA in November 2007, assessment of modification or prevention of exacerbations of disease can include severity of exacerbations as a primary efficacy endpoint. This can be based on worsening of symptoms requiring changes in treatment or requiring urgent treatment or hospitalisation. On a post hoc basis, rates of hospitalisation, corticosteroid use and a review of the medications used to treat the episodes of acute bronchitis were all analysed as measures of severity of episodes

ACTRN12606000076572 2013

Methods	Participants will be randomly allocated to active tablets each containing 45 mg HI-1-164-AS (inactivated non-typeable *Haemophilus influenzae*). Study medication (2 tablets) will be taken on days 1, 2, 3, 29, 30,31, 57, 58, 59. The live phase of the study will be of 8 months duration (March to October)
Participants	Both males and females, greater than or equal to 18 years of age, with mild to severe airway disease Total number of participants is 124; randomised to either active or placebo groups
Interventions	HI-1-164-AS (inactivated non-typeable *Haemophilus influenzae*) oral vaccine tablet
Outcomes	*Primary outcomes*: number of episodes of acute bronchitis during the study; proportion of participants experiencing an episode of acute bronchitis during the study; duration of episodes of acute bronchitis during the study; number of courses of antibiotics taken for treatment of acute episodes of bronchitis during the study *Secondary outcomes*: NTHi-specific antibody; pharyngeal colonisation with *Haemophilus influenzae* (*H. influenzae*); presence of *H. influenzae*, *M. catarrhalis*, *S. pneumoniae* and *Pseudomonas* species in sputum; severity of episodes of acute bronchitis
Notes	This trial is synonymous to ACTRN12606000074594 2013, with the only difference to be found in the inclusion criteria of participants; this trial accepts patients with mild to severe airway disease (versus moderate to severe), however, there is no further specification or discussion on how the investigators discern the extent of airway disease in their participants. Both studies enrolled participants on 7 March 2006 and were conducted simultaneously

ACTRN12610000916044 2013

Methods	Participants will be asked to take the study medication on 3 consecutive days each month for the first 3 months (that is, 9 doses in total). Each daily dose of HI-164OV contains 90 mg of HI-164 and will be taken orally approximately 1 hour prior to breakfast
Participants	Both males and females, from 40 to 85 years of age, with moderate to severe COPD Total number of participants is 340; randomised to either active or placebo groups
Interventions	Oral vaccine tablet containing 45 mg HI-164 active product
Outcomes	*Primary outcomes*: the primary endpoint is the rate of exacerbations requiring oral/parenteral corticosteroid treatment or hospitalisation. Patients will maintain daily diaries to record the severity of respiratory symptoms and the need for medications. Episodes of acute exacerbations, medication usage and COPD-related clinic or hospital visits will be recorded at each study visit. The rate of exacerbations will be measured in number of days since study entry to start of treatment or hospitalisation *Secondary outcomes*: proportion of participants per group experiencing exacerbations requiring oral/parenteral corticosteroid treatment or hospitalisation since study entry; time to systemic corticosteroid use or hospitalisation, or time to antibiotic use (separately and collectively) as measured in number of days from study entry to start of treatment; usage of antibiotics over the course of the study measured as total days usage, total number of courses and number of acute exacerbation events requiring 3 or more courses of antibiotics; use of oral/parenteral corticosteroid therapy for COPD exacerbations as measured by the total number of courses and total number of days of usage since study entry; total number of acute COPD exacerbations defined as mild, moderate or severe
Notes	Acute COPD exacerbations are defined as sustained (2 or more days) worsening or new onset of respiratory symptoms, particularly cough, purulent sputum and breathlessness, from steady state and beyond normal day to day variation that is acute in onset and necessitates a change in medication. Severity of exacerbations is based on the GOLD COPD classification of severity. Proportion of participants having recurrent (more than 1) COPD exacerbation. Acute exacerbations will be considered distinct events if onset dates are 7 or more days after resolution of symptoms defining the previous exacerbation; severity of acute exacerbations (mild, moderate or severe) based on the GOLD COPD classification system. Duration of acute COPD exacerbations in number of days from onset until resolution of symptoms. The duration in number of days of moderate and severe COPD exacerbations. The number and duration of hospitalisations, measured as total number of hospitalisations since study entry, total number of days per hospitalisation and total number of days hospitalisation since study entry. Total number of unscheduled visits to a physician and to the emergency department due to a COPD exacerbation since study entry. Change in forced expiratory volume in one second (FEV_1) from study entry based on spirometry (lung function test) measurement at each study visit. Change in quality of life based on the St George's Respiratory Questionnaire for COPD patients. Safety of HI-164OV based on adverse events (e.g. nausea, diarrhoea), vital signs (blood pressure, pulse, respiration rate), ECG and laboratory results

COPD: chronic obstructive pulmonary disease
ECG: electrocardiogram
FDA: Food and drug administration (United States)
GOLD: global initiative for chronic obstructive lung disease; organisation responsible for classifying and defining stages of COPD

DATA AND ANALYSES

Comparison 1. Primary outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Exacerbations (number of exacerbations/person)	6	557	Rate Ratio (Fixed, 95% CI)	0.97 [0.84, 1.12]
2 Mortality (deaths during trial period)	5	518	Odds Ratio (M-H, Fixed, 95% CI)	1.62 [0.63, 4.12]

Comparison 2. Secondary outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Prescriptions (number of courses/person/year)	3	142	Rate Ratio (Fixed, 95% CI)	1.81 [1.35, 2.44]
2 Hospital admissions (number of patients hospitalised during trial period)	2	358	Odds Ratio (M-H, Random, 95% CI)	0.96 [0.13, 7.04]
3 Adverse events (number of adverse events/person)	4	484	Rate Ratio (Fixed, 95% CI)	1.43 [0.70, 2.92]

Analysis 1.1. Comparison 1 Primary outcomes, Outcome 1 Exacerbations (number of exacerbations/person).

Review: *Haemophilus influenzae* oral vaccination for preventing acute exacerbations of chronic bronchitis and chronic obstructive pulmonary disease

Comparison: 1 Primary outcomes

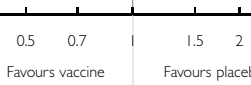
Outcome: 1 Exacerbations (number of exacerbations/person)

Study or subgroup	Vaccine N	Placebo N	log [Rate Ratio] (SE)	Rate Ratio IV,Fixed,95% CI	Weight	Rate Ratio IV,Fixed,95% CI
Clancy 1985	17	16	-2.626 (1.038)		0.5 %	0.07 [0.01, 0.55]
Clancy 1990	20	20	-0.531 (0.398)		3.5 %	0.59 [0.27, 1.28]
Tandon 1991	31	33	-0.309 (0.257)		8.3 %	0.73 [0.44, 1.21]
Lehmann 1991	30	32	-0.241 (0.259)		8.2 %	0.79 [0.47, 1.31]
Tandon 2010	18	20	-0.174 (0.281)		7.0 %	0.84 [0.48, 1.46]
Clancy 2013	160	160	0.081 (0.087)		72.6 %	1.08 [0.91, 1.29]
Total (95% CI)	**276**	**281**			**100.0 %**	**0.97 [0.84, 1.12]**

Heterogeneity: Chi^2 = 11.57, df = 5 (P = 0.04); I^2 =57%

Test for overall effect: Z = 0.41 (P = 0.68)

Test for subgroup differences: Not applicable

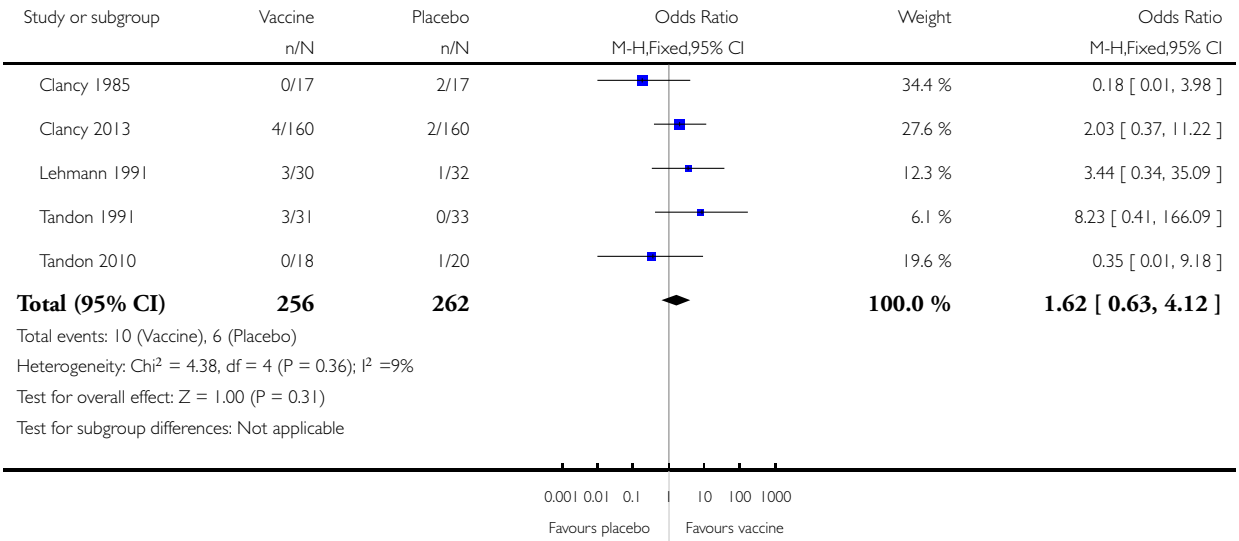


Analysis 1.2. Comparison 1 Primary outcomes, Outcome 2 Mortality (deaths during trial period).

Review: *Haemophilus influenzae* oral vaccination for preventing acute exacerbations of chronic bronchitis and chronic obstructive pulmonary disease

Comparison: 1 Primary outcomes

Outcome: 2 Mortality (deaths during trial period)



Analysis 2.1. Comparison 2 Secondary outcomes, Outcome 1 Prescriptions (number of courses/person/year).

Review: *Haemophilus influenzae* oral vaccination for preventing acute exacerbations of chronic bronchitis and chronic obstructive pulmonary disease

Comparison: 2 Secondary outcomes

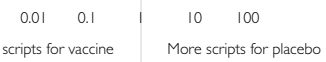
Outcome: 1 Prescriptions (number of courses/person/year)

Study or subgroup	Vaccine N	Placebo N	log [Rate Ratio] (SE)	Rate Ratio IV,Fixed,95% CI	Weight	Rate Ratio IV,Fixed,95% CI
Clancy 1990	20	20	0.397 (0.754)		4.0 %	1.49 [0.34, 6.52]
Tandon 1991	31	33	0.501 (0.187)		64.9 %	1.65 [1.14, 2.38]
Tandon 2010	18	20	0.817 (0.27)		31.1 %	2.26 [1.33, 3.84]
Total (95% CI)	**69**	**73**			**100.0 %**	**1.81 [1.35, 2.44]**

Heterogeneity: Chi^2 = 1.00, df = 2 (P = 0.61); I^2 =0.0%

Test for overall effect: Z = 3.95 (P = 0.000078)

Test for subgroup differences: Not applicable



Analysis 2.2. Comparison 2 Secondary outcomes, Outcome 2 Hospital admissions (number of patients hospitalised during trial period).

Review: *Haemophilus influenzae* oral vaccination for preventing acute exacerbations of chronic bronchitis and chronic obstructive pulmonary disease

Comparison: 2 Secondary outcomes

Outcome: 2 Hospital admissions (number of patients hospitalised during trial period)

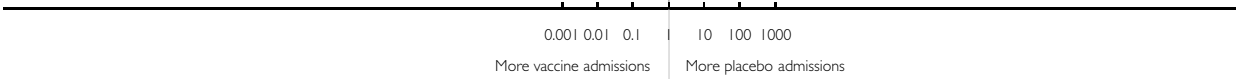
Study or subgroup	Vaccine n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Clancy 2013	80/160	48/160		56.6 %	2.33 [1.47, 3.69]
Tandon 2010	3/18	8/20		43.4 %	0.30 [0.07, 1.38]
Total (95% CI)	**178**	**180**		**100.0 %**	**0.96 [0.13, 7.04]**

Total events: 83 (Vaccine), 56 (Placebo)

Heterogeneity: $Tau^2 = 1.78$; $Chi^2 = 6.36$, df = 1 (P = 0.01); $I^2 = 84\%$

Test for overall effect: Z = 0.04 (P = 0.97)

Test for subgroup differences: Not applicable

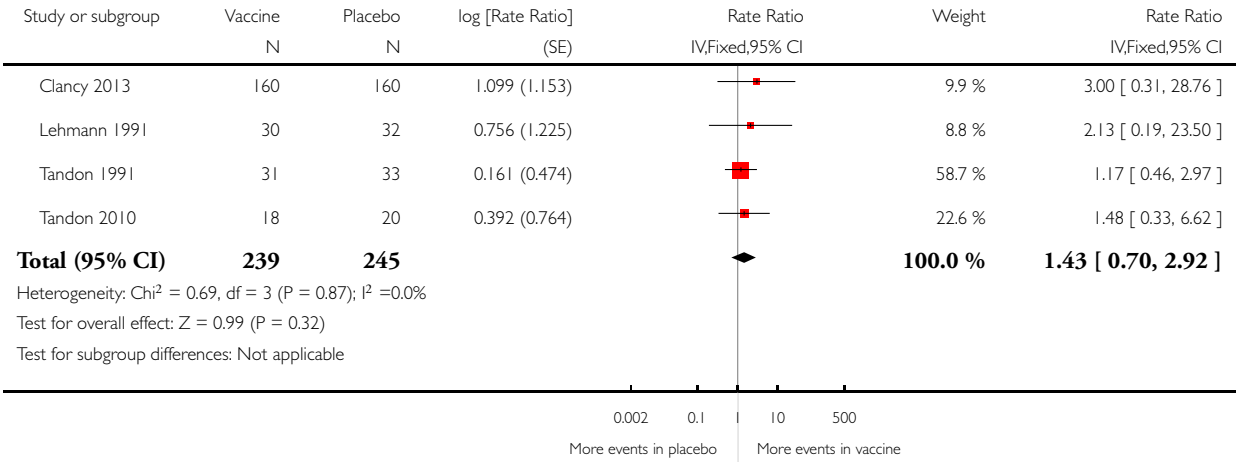


Analysis 2.3. Comparison 2 Secondary outcomes, Outcome 3 Adverse events (number of adverse events/person).

Review: *Haemophilus influenzae* oral vaccination for preventing acute exacerbations of chronic bronchitis and chronic obstructive pulmonary disease

Comparison: 2 Secondary outcomes

Outcome: 3 Adverse events (number of adverse events/person)



ADDITIONAL TABLES

Table 1. Rate estimates of acute exacerbations across included studies

Study	Vaccinated	Placebo	Absolute rate difference
Clancy 1985	0.256	0.272	0.016 (-)
Clancy 1990	1.000	1.700	0.700 (-)
Clancy 2013	0.717	0.767	0.050 (-)
Lehmann 1991	0.800	1.210	0.410 (-)
Tandon 1991	3.355	4.364	1.009 (-)
Tandon 2010	3.667	4.350	0.683 (-)
Overall mean	*1.633*	*2.111*	*0.478 (-)*

Estimated rate of exacerbation calculated as number of exacerbations per person per year.
Refer to Analysis 1.1: *Forest plot comparison and rate ratios for exacerbations*.

Table 2. Rate estimates of antibiotic prescriptions across included studies

Study	Vaccinated	Placebo	Absolute rate difference
Clancy 1990	0.500	1.200	0.700 (-)
Tandon 1991	5.806	10.194	4.388 (-)
Tandon 2010	3.180	7.200	4.020 (-)
Overall mean	*3.162*	*6.198*	*3.036 (-)*

Estimated rate of antibiotic prescriptions calculated as number of antibiotic courses per person per year.
Refer to Analysis 2.1: *Forest plot comparison and rate ratios for antibiotic prescriptions*.

Table 3. Rate estimates of adverse events across included studies

Study	Vaccinated	Placebo	Absolute rate difference
Clancy 2013	0.008	0.025	0.017 (-)
Lehmann 1991	0.067	0.031	0.036 (+)
Tandon 1991	1.032	1.212	0.180 (-)
Tandon 2010	0.167	0.450	0.283 (-)
Overall mean	*0.319*	*0.430*	*0.111 (-)*

Estimated rate of adverse events calculated as number of adverse events per person per year.
Refer to Analysis 2.3: *Forest plot comparison and rate ratios for adverse events*.

APPENDICES

Appendix 1. MEDLINE and CENTRAL search strategy

MEDLINE (Ovid)

1 exp Bronchitis/
2 bronchit*.tw.
3 exp Pulmonary Disease, Chronic Obstructive/
4 (chronic obstructive pulmonary disease* or chronic obstructive lung disease*).tw.
5 Lung Diseases, Obstructive/
6 (copd or aecb).tw.
7 or/1-6
8 exp Haemophilus influenzae/
9 (haemophilus influenz* or "h. influenzae").tw.
10 (hemophilus or haemophilus).tw.
11 nthi.tw.
12 or/8-11
13 exp Vaccines/
14 exp Immunization/
15 Immunotherapy/
16 (vaccin* or immuni* or inoculat*).tw.
17 or/13-16
18 12 and 17
19 Haemophilus Vaccines/
20 18 or 19
21 7 and 20

Appendix 2. EMBASE (Elsevier) search strategy

#27 #18 AND #26
#26 #21 NOT #25
#25 #22 NOT #24
#24 #22 AND #23
#23 'human'/de
#22 'animal'/de OR 'nonhuman'/de OR 'animal experiment'/de
#21 #19 OR #20
#20 random*:ab,ti OR placebo*:ab,ti OR crossover*:ab,ti OR 'cross over':ab,ti OR allocat*:ab,ti OR trial:ti OR (doubl* NEXT/1 blind*):ab,ti
#19 'randomized controlled trial'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp
#18 #5 AND #17
#17 #15 OR #16
#16 'haemophilus vaccine'/de
#15 #9 AND #14
#14 #10 OR #11 OR #12 OR #13
#13 vaccin*:ab,ti OR immuni*:ab,ti OR inoculat*:ab,ti
#12 'immunotherapy'/de
#11 'immunization'/exp
#10 'vaccine'/exp
#9 #6 OR #7 OR #8
#8 haemophilus:ab,ti OR hemophilus:ab,ti
#7 'haemophilus influezae':ab,ti OR 'h. influenzae':ab,ti OR nthi:ab,ti

#6 'haemophilus influenzae'/exp
#5 #1 OR #2 OR #3 OR #4
#4 'chronic obstructive lung disease':ab,ti OR 'chronic obstructive pulmonary disease':ab,ti OR copd:ab,ti OR aecb:ab,ti
#3 'chronic obstructive lung disease'/de
#2 bronchit*:ab,ti
#1 'bronchitis'/exp

Appendix 3. CINAHL (Ebsco) search strategy

S18 S6 and S17
S17 S15 or S16
S16 (MH "HIB Vaccine")
S15 S9 and S14
S14 S10 or S11 or S12 or S13
S13 TI (vaccin* or immuni* or inocul*) OR AB (vaccin* or immuni* or inocul*)
S12 (MH "Immunotherapy")
S11 (MH "Immunization+")
S10 (MH "Vaccines+")
S9 S7 or S8
S8 TI (haemophilus or hemophilus or "h. influenzae" or nthi) OR AB (haemophilus or hemophilus or "h. influenzae" or nthi)
S7 (MH "Haemophilus Influenzae")
S6 S1 or S2 or S3 or S4 or S5
S5 TI (chronic obstructive pulmonary disease* or chronic obstructive airway* disease* or chronic obstructive lung disease* or coad or copd or aecb) OR AB (chronic obstructive pulmonary disease* or chronic obstructive airway* disease* or chronic obstructive lung disease* or coad or copd or aecb)
S4 (MH "Lung Diseases, Obstructive")
S3 (MH "Pulmonary Disease, Chronic Obstructive+")
S2 TI bronchit* OR AB bronchit*
S1 (MH "Bronchitis+")

Appendix 4. LILACS (BIREME) search strategy

Search > (MH:Bronchitis OR MH:C08.127.446$ OR MH:C08.381.495.146$ OR C08.730.099$ OR Bronquitis OR Bronquite OR bronchit$ OR MH:"Pulmonary Disease, Chronic Obstructive" OR "Chronic Obstructive Airway Disease" OR "Chronic Obstructive Lung Disease" OR "Chronic Obstructive Pulmonary Disease" OR COAD OR COPD OR MH:C08.381.495.389$ OR "Obstrucción Crónica del Flujo Aéreo" OR "Obstrucción del Flujo Aéreo Crónica" OR "Enfermedad Obstructiva Crónica de las Vías Aéreas" OR "Enfermedad del Pulmón Crónica Obstructiva" OR "Enfermedad Pulmonar Crónica Obstructiva" OR EVOC OR EPOC OR "Neumopatía Obstructiva Crónica" OR DPOC OR "Obstrução Crônica do Fluxo Respiratório" OR "Obstrução do Fluxo Respiratório Crônica" OR "Doença Obstrutiva Crônica das Vias Aéreas" OR "Doença Obstrutiva Crônica do Pulmão" OR "Doença Obstrutiva Crônica Pulmonar" OR MH:"Lung Diseases, Obstructive" OR AECB) AND (((MH:"Haemophilus influenzae" OR "H. influenzae" OR haemophilus OR hemophilus OR nthi OR MH:B03.440.450.600.450.330$ OR MH:B03.660.250.550.290.330$) AND (MH: Vaccines OR Vacunas OR Vacinas OR vaccin$ OR D20.215.894$ OR MH:Immunization OR Inmunización OR Imunização OR MH:E02.095.465.425.400$ OR MH:E05.478.550$ OR MH:N02.421.726.758.310$ OR MH:N06.850.780.200.425$ OR MH: N06.850.780.680.310$ OR MH:SP2.026.182.113$ OR MH:SP4.001.002.015.049$ OR MH:SP8.946.819.838$ OR "Estimulación Inmunológica" OR Inmunoestimulación OR "Sensibilización Inmunológica" OR Variolación OR Variolización OR Inmunizaciones OR "Estimulação Imunológica" OR Imunoestimulação OR "Sensibilização Imunológica" OR Variolação OR Imunizações OR immuni$ OR MH:Immunotherapy OR Inmunoterapia OR Imunoterapia OR inocul$)) OR (MH:"Haemophilus Vaccines" OR "Vacunas contra Haemophilus" OR "Vacinas Anti-Haemophilus"))

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

# 5	**18**	#4 AND #3 *Databases=SCI-EXPANDED, CPCI-S Timespan=All Years* *Lemmatization=On*
# 4	**1,371,720**	Topic=(random* or placebo* or "clinical trial*" or ((singl* or doubl*) NEAR/1 blind*) or allocat* or crossover* or "cross over") OR Title=(trial*) *Databases=SCI-EXPANDED, CPCI-S Timespan=All Years* *Lemmatization=On*
# 3	**117**	#2 AND #1 *Databases=SCI-EXPANDED, CPCI-S Timespan=All Years* *Lemmatization=On*
# 2	**5,029**	Topic=(hemophilus or haemophilus or "h. influenzae" or nthi) AND Topic=(vaccin* or immuni* or inocul*) *Databases=SCI-EXPANDED, CPCI-S Timespan=All Years* *Lemmatization=On*
# 1	**42,910**	Topic=(bronchit* or "chronic obstructive pulmonary disease*" or "chronic obstructive airway* disease*" or "chronic obstructive lung disease*" or coad or copd or aecb) *Databases=SCI-EXPANDED, CPCI-S Timespan=All Years* *Lemmatization=On*

CONTRIBUTIONS OF AUTHORS

All of the authors contributed to the drafting of the protocol. Professor Mieke van Driel and Professor Allan Cripps provided expert and methodological advice, including extensive help and support during the drafting of the protocol and review.

DECLARATIONS OF INTEREST

Professor Allan Cripps was involved in the initial animal work and conduct of the four trials in Newcastle, Australia. The commercial product, 'Bronchostat', which originated from these trials, is no longer commercially available. The commercial companies Auspharm International Limited and subsequently Cortecs International Limited have ceased trading and were delisted from the Australian Stock Exchange (ASX) in 1991 and 1998 respectively. Prior to 1996, Professor Cripps acted as a consultant for both Auspharm International Limited and Cortecs International Limited. Hunter Immunology Limited subsequently continued development of the oral whole cell vaccine (HI-164). In 2004 Professor Cripps acquired a small stock holding in the company. In 2011, Hunter immunology Limited was acquired by Bioxyne Limited and his shares were transferred to Bioxyne Limited. Subsequently, in February 2014 Bioxyne Limited sold to Mariposa Health Limited, the HI-164 Oral Vaccine project and all associated intellectual property. Should Mariposa Health Limited successfully commercialise the vaccine, Mariposa Health Limited have agreed to pay Bioxyne Limited a Royalty of up to 6.5% of gross revenue. Professor Cripps retains a small residual stock holding in Bioxyne Limited. Professor Cripps has no stock holding in

Mariposa Health Limited. He has not received any honoraria, participated in expert testimony or received any consultancy fees from either Mariposa Health Limited or Bioxyne Limited. Professor Cripps' potential conflicts of interest have been assessed by the Cochrane Funding and Arbitration Panel (reference number 150514/064) and considered of low risk.

Edward Teo has no potential conflicts of interest to declare.

Hugh House has no potential conflicts of interest to declare.

Kathleen Lockhart has no potential conflicts of interest to declare.

Sai Navya Purchuri has no potential conflicts of interest to declare.

Jennifer Pushparajah has no potential conflicts of interest to declare.

Mieke L van Driel has no potential conflicts of interest to declare.

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- Griffith University, Australia.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Risk ratios have been included as a method of measuring the treatment effect for dichotomous data given as rates. We have amended the Data synthesis to reflect that we have also used the fixed-effect model to pool study data that reported events as rates.

Prescriptions of corticosteroids were not an outcome measure in any of the included studies and therefore not part of this review's analyses. However, patients were noted to have been prescribed steroids prior to commencing the trial and may have continued steroids or have been further prescribed steroids during the trial periods without clear reporting in the studies (this is discussed in the Summary of main results).

Number of hospital admissions was added to Secondary outcomes as part of the assessment of the severity of exacerbations after post hoc analysis revealed that a number of studies reported hospital admissions.