

Influenza vaccine for children and adults with bronchiectasis (Review)

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[Intervention Review]

Influenza vaccine for children and adults with bronchiectasis

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ABSTRACT

Background

Bronchiectasis is a major cause of respiratory morbidity especially in developing countries. In affluent countries, bronchiectasis is increasingly recognised in certain subsections of communities (e.g. Aboriginal communities) as well as a coexistent disease/comorbidity and disease modifier in respiratory diseases such as COPD (reported rates of 29-50% in adults). Respiratory exacerbations in people with bronchiectasis are associated with reduced quality of life, accelerated pulmonary decline, hospitalisation and even death. Current recommendations for inactivated influenza vaccination includes adults aged 65 years and over, those in residential care and health care workers and also all adults and children with chronic illness, particularly cardiac and pulmonary diseases.

Objectives

To evaluate the effectiveness of influenza vaccine as routine management in children and adults with bronchiectasis in (a) reducing the severity and frequency of respiratory exacerbations and (b) pulmonary decline

Search strategy

The Cochrane Register of Controlled Trials (CENTRAL), the Cochrane Airways Group Specialised Register, MEDLINE and EMBASE databases were searched by the Cochrane Airways Group. Pharmaceutical manufacturers of influenza were also contacted. The latest searches were performed in July 2006.

Selection criteria

All randomised controlled trials with at least one annual influenza vaccine involving children or adults with bronchiectasis.

Data collection and analysis

Results of searches were reviewed against pre-determined criteria for inclusion. It was planned that two independent reviewers selected, extracted and assessed data for inclusion.

Main results

No eligible trials were identified and thus no data were available for analysis.

Authors' conclusions

There is neither evidence for, nor against, routine annual influenza vaccination for children and adults with bronchiectasis.

PLAIN LANGUAGE SUMMARY

Influenza vaccine for children and adults with bronchiectasis

In many countries, influenza vaccination is an accepted part of routine immunisation recommendations particularly in persons 65 years and over, those in long-term care facilities and also adults and children with chronic illnesses including those with bronchiectasis. In this review however, our search for randomised control trials examining the effectiveness of influenza vaccines for people with bronchiectasis revealed no relevant studies. In the absence of evidence, patients' needs should be individualised and national guidelines be adhered to.

BACKGROUND

Bronchiectasis, previously termed an 'orphan disease' is increasingly recognized as a major cause of respiratory morbidity especially in developing countries (Karadag 2005, Karakoc 2001) and in pockets of affluent countries (Singleton 2000, Callahan 2002, Edwards 2003). The underlying aetiology of bronchiectasis varies from post recurrent respiratory infections to rare immune deficiencies. A variety of diseases including the common chronic obstructive pulmonary disease (COPD) (Patel 2004) and less common respiratory diseases (e.g. bronchiolitis obliterans (Chang 1998) and sarcoidosis (Lewis 2002)) and even non-primary respiratory (e.g. autoimmune) diseases may culminate in the development of bronchiectasis. The presence of bronchiectasis increases the morbidity and mortality of the underlying primary disease (Patel 2004, Lewis 2002, Keistinen 1997). For example, bronchiectasis has been reported in 29-50% of COPD (Patel 2004, O'Brien 2000) and when present, increases the severity (Patel 2004) and frequency (Gursel 2006) of respiratory exacerbations. Thus, management of the symptoms and severity of bronchiectasis is important.

The dominant symptoms and signs of bronchiectasis are productive or wet cough, dyspnoea on exertion and presence of other respiratory signs (clubbing, chest wall deformity, respiratory noises such as wheeze or crepitations on auscultation). In the long term, pulmonary decline may occur (Keistinen 1997, Twiss 2006). Like patients with COPD, children and adults with bronchiectasis also suffer from recurrent acute exacerbations, some of which require hospitalised treatment. Effective management regimes for bronchiectasis aim to reduce the frequency and severity of respiratory exacerbations and the rate long term pulmonary decline. Based on Cole's 'vicious circle hypothesis', microbial colonization/

infection is important in the pathophysiology of bronchiectasis as it leads to bronchial obstruction and a normal or exaggerated inflammatory response (Cole 1986). Thus treatment modalities that prevent or limit respiratory infections would prevent or reduce respiratory decline. Respiratory infections also increase morbidity and reduces quality of life in those suffering bronchiectasis (Martinez-Garcia 2005). Theoretically prevention of influenza through the use of influenza vaccine would be a useful routine management modality for children and adults with bronchiectasis. Indeed yearly influenza vaccination is recommended for patients with bronchiectasis (Chang 2002).

Both inactivated and live attenuated (LAIV) influenza vaccine are now available. Both are annually modified trivalent vaccines with adjustments for each of the major circulating influenza viruses: A (H3N2), A (H1N1) and B and administered annually (Orenstein 2005). The efficacy is directly related to the degree of concordance between the virus strains included in the vaccine and the strains circulating in the community. The inactivated vaccine contains killed viruses and is administered via intramuscular route and is recommended in those 6 months and older, in healthy individuals and those with chronic medical conditions. The newer LAIV contains live virus with potential for replication and is currently only recommended in healthy individuals aged between 5 and 49 years (Orenstein 2005), thus contraindicated in those with bronchiectasis.

Current recommendations for inactivated influenza vaccination includes adults aged 65 years and over, those in residential care and health care workers and also all adults and children with chronic illness, particularly cardiac and pulmonary diseases. Influenza vac-

cine has been estimated to be 70-90% effective in preventing influenza in healthy individuals under 65 years of age, with some reduction in efficacy in the elderly (Orenstein 2005). A meta-analysis of 20 cohort studies involving both nursing home populations and community-dwelling elderly estimated effectiveness of 56%, 53%, 50% and 68% for preventing respiratory illness, pneumonia, hospitalisation and death, respectively. The efficacy of influenza vaccination in children is less known, though it has been estimated to provide 56% or more protection (Orenstein 2005, Fukuda 2004). The effect of influenza vaccine in preventing asthma exacerbations related to influenza is uncertain in patients with asthma (Cates 2003). In another Cochrane review, Poole and colleagues concluded that influenza vaccination reduces respiratory exacerbations in patients with COPD (Poole 2006). The effect size described in the meta-analysis of RCTs was similar to that of observational studies (Poole 2006).

The triggers for bronchiectasis exacerbations are less well studied compared to the available data on triggers of exacerbations for asthma and COPD. The proportion of bronchiectasis exacerbations triggered by infections is uncertain, much less the culprit microbiological organism. The effectiveness of influenza vaccination for bronchiectasis may thus, be rather different to that for asthma and COPD. Influenza vaccination may be associated with local and systemic adverse events including a flu-like illness (Poole 2006). A systematic review of the effectiveness of influenza for children and adults with bronchiectasis would be beneficial to guide clinical practice.

OBJECTIVES

To evaluate the effectiveness of influenza vaccine as routine management in children and adults with bronchiectasis in (a) reducing the severity and frequency of respiratory exacerbations and (b) pulmonary decline

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials using influenza vaccine in patients with bronchiectasis

Types of participants

Children or adults with bronchiectasis (defined clinically or radiologically)

Exclusion criteria: Participants with cystic fibrosis or other diseases where bronchiectasis is not present

Types of interventions

All randomised controlled trials with at least one annual influenza vaccine. All types of influenza vaccines were to be included.

Types of outcome measures

It was planned that attempts would have been made to obtain data on at least one of the following outcome measures:

- (A) for short term effectiveness (12 months or less)
- proportions of participants who had respiratory exacerbations
 - proportions of participants who were hospitalised,
 - total numbers of days with respiratory symptoms
 - total number of hospitalised days
 - mean difference in bronchiectasis severity control (QOL, cough diary, Likert scale, visual analogue scale, level of interference of cough, cough diary, etc),
 - proportions experiencing adverse effects of the intervention, (e.g. local reaction, exacerbation immediately post vaccination, systemic effects (myalgia, fever, fatigue), Guillain-Barre syndrome, etc)
- Outcomes (a) to (e) were to be examined globally as well as also specifically to proven influenza infections (from swabs or rising titres)
- (B) for medium to long term outcomes (>1 year)
- radiology scores (high resolution computed tomography scans or chest radiograph)
 - lung function
 - clinical indices of bronchiectasis severity control (QOL, cough diary, Likert scale, visual analogue scale, level of interference of cough, etc),
 - relevant airway markers of inflammation.

Search methods for identification of studies

The following topic search strategy were used to identify the relevant randomised controlled trials listed on the electronic databases (Table 1):

Trials were identified from the following sources:

- The Cochrane Airways Group Specialised Trials Register
- The Cochrane Central Register of Controlled Trials (CENTRAL)
- MEDLINE (1966 to present). Topic search strategy combined with the RCT search filter as outlined in the Airways Group module.
- OLDMEDLINE (1950 to 1965). Topic search strategy combined with the RCT search filter as outlined in the Airways Group module.

5. EMBASE (1980 to present). Topic search strategy combined with the RCT search filter as outlined in the Airways Group module.

6. The list of references in relevant publications.

7. Written communication with the authors of trials would have been included in the review if necessary.

8. Pharmaceutical companies that manufacture influenza vaccines.

Table 1. Database search strategy

Central	Medline/Old medline	EMBASE
#1 MeSH descriptor Bronchiectasis explode all trees in MeSH products	1. exp bronchiectasis/	1. exp BRONCHIECTASIS/
#2 bronchiect*	2. bronchiect\$.mp.	2. bronchiect\$.mp.
#3 suppurativ* near lung*	3. (suppurativ\$ adj5 lung\$).mp.	3. (suppurativ\$ adj5 lung\$).mp.
#4 bronch* near dilat*	4. (bronch\$ adj5 dilat\$).mp.	4. (bronch\$ adj5 dilat\$).mp.
#5 (#1 OR #2 OR #3 OR #4)	5. or/1-4	5. or/1-4
#6 MeSH descriptor Influenza, Human explode all trees in MeSH products	6. exp Influenza Vaccines/	6. exp Influenza Vaccine/
#7 influenza*	7. flumist.mp.	7. flumist.mp.
#8 flu	8. trivalent.mp.	8. trivalent.mp.
#9 MeSH descriptor Influenza Vaccines explode all trees in MeSH products	9. LAIV.mp.	9. LAIV.mp.
#10 MeSH descriptor Immunization explode all trees in MeSH products	10. CAIV.mp.	10. CAIV.mp.
#11 MeSH descriptor Vaccines explode all trees in MeSH products	11. medimmune.mp.	11. medimmune.mp.
#12 vaccin*	12. exp Influenza, Human/	12. exp Influenza/
#13 immuni*	13. influenza.mp.	13. influenza.mp.
#14 flumist	14. flu.mp.	14. flu.mp.
#15 trivalent	15. exp immunization/	15. exp Vaccine/
#16 LAIV	16. exp vaccines/	16. exp immunization/
#17 medimmune	17. vaccinat\$.mp.	17. vaccin\$.mp.
#18 CAIV	18. immuni\$.mp.	18. immuni\$.mp.
#19 (#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18)	19. or/6-18	19. or/6-18
#20 (#19 AND #5)	20. 19 and 5	20. 19 and 5

Data collection and analysis

Retrieval of studies: From the title, abstract, or descriptors, two reviewers independently reviewed literature searches to identify potentially relevant trials for full review. Searches of bibliographies and texts were conducted to identify additional studies. From the full text using specific criteria, the same two reviewers independently selected trials for inclusion. Agreement would have been measured using kappa statistics. Disagreement would have been resolved by consensus.

It was planned that trials that satisfied the inclusion criteria would have been reviewed and the following information recorded: study setting, year of study, source of funding, patient recruitment details (including number of eligible subjects), inclusion and exclusion criteria, other symptoms, randomisation and allocation concealment method, numbers of participants randomised, blinding (masking) of participants, care providers and outcome assessors, dose and type of intervention, duration of therapy, co-interventions, numbers of patients not followed up, reasons for withdrawals from study protocol (clinical, side-effects, refusal and other), details on side-effects of therapy, and whether intention-to-treat analyses were possible. Data would have been extracted on the outcomes described previously. Further information would have been requested from the authors when required.

Studies included in the review would have undergone quality assessment performed independently by 2 reviewers. Four components of quality would have been assessed:

1. Allocation concealment. Trials would have been scored as: Grade A: Adequate concealment, Grade B: Unclear, Grade C: Clearly inadequate concealment. (Grade A = high quality).
2. Blinding. Trials would have been scored as: Grade A: Participant and care provider and outcome assessor blinded, Grade B: Outcome assessor blinded, Grade C: Unclear, Grade D: No blinding of outcome assessor (Grade A, B = high quality).
3. Reporting of participants by allocated group. Trials would have been scored as: Grade A: The progress of all randomised children in each group described, Grade B: Unclear or no mention of withdrawals or dropouts, Grade C: The progress of all randomised children in each group clearly not described. (Grade A = high quality).
4. Follow-up. Trials would have been scored as: Grade A: Outcomes measured in >90% (where withdrawals due to complications and side-effects are categorised as treatment failures), Grade B: Outcomes measured in 80-90%, Grade C: Unclear, Grade D: Outcomes measured in <80%. (Grade A = high quality).

While only the allocation concealment quality assessment would have been displayed in the meta-analysis figures, all assessments would have been included in the "Characteristics of included studies" table. Inter-reviewer reliability for the identification of high quality studies for each component would have been measured by the Kappa statistic.

STATISTICS

For the dichotomous outcome variables of each individual study,

odds ratio (OR) would have been calculated using a modified intention-to-treat analysis. This analysis assumes that children not available for outcome assessment have not improved (and probably represents a conservative estimate of effect). An initial qualitative comparison of all the individually analysed studies of all the individually analysed studies examine whether pooling of results (meta-analysis) is reasonable. This would take into account differences in study populations, inclusion/exclusion criteria, interventions, outcome assessment, and estimated effect size.

It was planned that the results from studies that met the inclusion criteria and reported any of the outcomes of interest would have been included in the subsequent meta-analyses. The summary weighted risk ratio and 95% confidence interval (fixed effects model) would have been calculated (Cochrane statistical package, RevMan version 4.2). For cross-over studies, mean treatment differences would have been calculated from raw data, extracted or imputed and entered as fixed effects generic inverse variance (GIV) outcome, to provide summary weighted differences and 95% confidence intervals. In cross-over trials, only data from the first arm would have been included in meta analysis if data were combined with parallel studies (Elbourne 2002). Numbers needed to treat (NNT) would have been calculated from the pooled OR and its 95% CI applied to a specified baseline risk using an online calculator (Cates 2003b). If studies reported outcomes using different measurement scales, the standardised mean difference would have been estimated. Any heterogeneity between the study results would have been described and tested to see if it reached statistical significance using a chi-squared test. The 95% confidence interval estimated using a random effects model would have been included whenever there are concerns about statistical heterogeneity.

SUB-GROUP ANALYSIS:

The following a priori sub-group analyses was planned:

1. children (aged 18 years or less) and adults (>18 years)
 2. types of influenza vaccine
 3. type of control group
 4. participant type (bronchiectasis as primary disease vs bronchiectasis as co-existent disease)
 5. severity of bronchiectasis (based on lung function)
- Sensitivity analyses were also planned to assess the impact of the potentially important factors on the overall outcomes:
- a) study quality;
 - b) study size;
 - c) variation in the inclusion criteria;
 - d) differences in the medications used in the intervention and comparison groups;
 - e) differences in outcome measures;
 - f) analysis using random effects model;
 - g) analysis by "treatment received"; and
 - h) analysis by "intention-to-treat".

RESULTS

Description of studies

See: [Characteristics of excluded studies](#).

The searches identified 4 potential publications, none fulfilled the study eligibility criteria.

Risk of bias in included studies

Not applicable

Effects of interventions

The Airways Group specialised register/search identified 289 potentially relevant titles. After assessing the abstracts, 4 publications were considered for inclusion into review including 2 non-English articles (French). None of the studies fulfilled study criteria. No additional studies were found in the review articles. No additional data were available from the five pharmaceutical companies contacted (CSL Limited, Sanofi Pasteur Pty Limited, Chiron Vaccines Australia Pty Ltd, GlaxoSmithKline Australia Pty Ltd, Solvay Pharmaceuticals).

DISCUSSION

No randomised controlled trials comparing any influenza vaccines in children or adults with bronchiectasis were identified.

Based on many rationales including the risk factors of severe influenza infections, yearly influenza vaccination is widely recommended for patients with chronic respiratory disorders ([Cosgrove 2005](#), [Jefferson 2006](#)). However there is no RCT evidence that has examined whether annual influenza vaccination is indeed beneficial in patients with bronchiectasis. The Cochrane review on influenza vaccination for patients with COPD described that “inactivated influenza vaccination has a clinically important and significant effect on influenza-related exacerbations, and probably an effect on the total of exacerbations in COPD patients” ([Poole 2006](#)). Given the wide overlap between COPD and bronchiectasis, where up to 50% of patients with COPD have coexistent bronchiectasis ([Patel 2004](#)), it is arguably justified that until new evidence to the contrary exist, patients with bronchiectasis should be routinely vaccinated. However influenza vaccinations are not without risks and adverse events although mostly minor, may be serious ([Wong 2005](#)). Thus, in the absence of good evidence for the benefits of annual routine influenza vaccination, individual preferences and risk factors for increased adverse events should be considered. Furthermore, the argument of policy versus evidence for influenza vaccination was recently elegantly discussed by Jefferson ([Jefferson 2006](#)).

In patients with asthma and COPD, Cochrane reviews have shown that inactivated influenza vaccinations do not cause an immediate respiratory exacerbation ([Cates 2003](#), [Poole 2006](#)). Whether immediate respiratory exacerbations is increased in patients with bronchiectasis post inactivated influenza vaccinations is unknown; it remains a theoretical risk in the context of the common occurrence of mild immune dysfunction in patients with bronchiectasis ([King 2006](#)). In the consideration of possible future uses of LAIV (which is currently used only in healthy individuals and hence not currently relevant in this target group), the risk of viral shedding for several days, especially in children ([Cosgrove 2005](#)) must also be taken into account.

AUTHORS' CONCLUSIONS

Implications for practice

There is neither evidence for nor against, routine annual influenza vaccination for children and adults with bronchiectasis. Given the recommendations of the Cochrane review on influenza vaccination in patients with COPD ([Poole 2006](#)), and the significant overlap between COPD and bronchiectasis, current recommendations for annual influenza vaccination in patients with bronchiectasis is justified. However, individual responses and risk for adverse effects need to be taken into account when considered for routine annual influenza vaccination.

Implications for research

Acknowledging the difficulty in conducting large, randomised, placebo-controlled trials of repeated influenza vaccination in patients with bronchiectasis, it would still appear desirable to do so. There is also little knowledge on the effects of annual revaccination in this target group. Multi-centre randomised controlled trials to establish the efficacy of influenza vaccination in reducing severity and frequency of respiratory exacerbations and pulmonary decline in people with bronchiectasis are needed. As responses to vaccines alters with age, cohorts should comprise of different age groups including young children (aged under 2 years), children, adults and older adults. Determining true influenza infections from the range of other influenza-like illnesses by microbiological and serological techniques is recommended.

ACKNOWLEDGEMENTS

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Wong 2005

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Hayden 1995	Pilot study to determine whether the use of structured guidelines for which pulmonary disorders warrant influenza vaccination increases use of vaccinations
King 2005	Observational study in adults with bronchiectasis
Lamotte 1981	Non RCT in French (review article)
Michel 1975	Study on children and adolescents with bronchiectasis using dietary supplements and anti-bacterial vaccine

DATA AND ANALYSES

This review has no analyses.

WHAT'S NEW

Last assessed as up-to-date: 17 April 2007.

12 March 2009	Amended	Contact details changed
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HISTORY

Protocol first published: Issue 4, 2006

Review first published: Issue 3, 2007

16 April 2008	Amended	Converted to new review format.
18 April 2007	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

CC and AC wrote the protocol and review, and selected relevant articles from the search. CC wrote to the pharmaceutical companies. PM reviewed the manuscript.

DECLARATIONS OF INTEREST

None declared.

INDEX TERMS

Medical Subject Headings (MeSH)

Bronchiectasis [*complications]; Influenza, Human [*prevention & control]; Influenza Vaccines [*administration & dosage]

MeSH check words

Adult; Child; Humans