

Pneumococcal vaccines for children and adults with bronchiectasis (Review)

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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
BACKGROUND	2
OBJECTIVES	3
METHODS	3
RESULTS	4
DISCUSSION	5
AUTHORS' CONCLUSIONS	5
ACKNOWLEDGEMENTS	5
REFERENCES	6
CHARACTERISTICS OF STUDIES	7
DATA AND ANALYSES	9
ADDITIONAL TABLES	9
WHAT'S NEW	10
HISTORY	10
CONTRIBUTIONS OF AUTHORS	10
DECLARATIONS OF INTEREST	11
SOURCES OF SUPPORT	11
INDEX TERMS	11

[Intervention Review]

Pneumococcal vaccines for children and adults with bronchiectasis

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ABSTRACT

Background

Bronchiectasis is increasingly recognized as a major cause of respiratory morbidity especially in developing countries. Even in affluent countries, bronchiectasis is increasingly seen in some community subsections (e.g. Aboriginal communities) and occurs as a comorbidity and disease modifier in respiratory diseases such as chronic obstructive pulmonary disease (COPD). Respiratory exacerbations in people with bronchiectasis are associated with reduced quality of life, accelerated pulmonary decline, hospitalisation and even death. Conjugate pneumococcal vaccine is part of the routine infant immunisation schedule in many countries. Current recommendations for additional pneumococcal vaccination include children and adults with chronic suppurative disease.

Objectives

To evaluate the effectiveness of pneumococcal 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 pneumococcal vaccines were also contacted. The latest searches were performed in November 2007.

Selection criteria

All randomised controlled trials that utilised pneumococcal vaccine on children and adults with bronchiectasis. All types of pneumococcal vaccines were included.

Data collection and analysis

Results of searches were reviewed against pre-determined criteria for inclusion. No eligible trials were identified and thus no data was available for analysis. One small non-randomised controlled trial in children was reported.

Main results

No randomised controlled trials pertaining effectiveness of pneumococcal vaccine as routine management in children and adults with bronchiectasis were found. A benefit in elimination of *Strep. pneumoniae* in the sputum was found in a non-randomised trial in children but no clinical effect was described.

Authors' conclusions

At present, there is a lack of reliable evidence to support or refute the routine use of pneumococcal vaccine as routine management in children and adults with bronchiectasis. Randomised controlled trials examining the efficacy of this intervention using various vaccine types in different age groups are needed. Until further evidence is available, it is recommended that health providers adhere to national guidelines.

PLAIN LANGUAGE SUMMARY

Pneumococcal vaccines for children and adults with bronchiectasis

In many countries vaccination for the protection against infection of the bacteria pneumococcus, is part of the immunisation schedule for infants as well as, for people with bronchiectasis. In this review, our search for randomised control trials that examined the effectiveness of pneumococcal vaccines for people with bronchiectasis revealed no relevant studies. We thus cannot draw any conclusions for, or against, the routine pneumococcal vaccinations in people with bronchiectasis. However, we would recommend that national guidelines be followed until further evidence is available.

BACKGROUND

Bronchiectasis, previously termed an 'orphan's disease' is increasingly recognized as a major cause of respiratory morbidity especially in developing countries (Karadag 2005) and in pockets of affluent countries (Edwards 2003, Singleton 2000). Of diverse aetiology, bronchiectasis is often a result of repeated respiratory infections or may be due to rare immune deficiencies. Increasingly recognised as a common final pathway for a variety of diseases, it is seen to complicate both common and uncommon respiratory illnesses such as COPD, bronchiolitis obliterans and sarcoidosis (Patel 2004, Chang 1998, Lewis 2002) and also secondary pulmonary illnesses such as autoimmune diseases. Its co-existence increases the morbidity and mortality of the underlying disease (Patel 2004, Lewis 2002, Keistinen 1997). For instance, bronchiectasis is reported to occur in 29-50% of COPD (Patel 2004, O'Brien 2000) and when present, increases the severity and frequency of respiratory exacerbations (Patel 2004, Gursel 2006). Thus, management of the symptoms and prevention of progression of bronchiectasis is important.

The dominant symptoms and signs of bronchiectasis are a 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). Children and adults with bronchiectasis suffer from recurrent acute exacerbations, some necessitating inpatient care. Effective management regimes for bronchiectasis should improve quality of life, reduce the frequency and severity of respiratory exacerbations and rate of pulmonary decline. Cole's 'vicious circle hypothesis' suggests microbial colonization or infection as a key factor in its pathophysiology as this often leads to bronchial obstruction and a normal or exaggerated inflammatory response (Cole 1986). Treatment modalities that prevent or limit respiratory infections should thus, prevent or reduce respiratory decline. Respiratory infection alone increases morbidity and reduces the quality of life in those with bronchiectasis (Martinez-Garcia 2005). Pneumococcal respiratory infections is a common respiratory pathogen in acute (Lucero 2004) and chronic respiratory diseases (Devitt 1977). Prevention of pneumococcal infections through the use of pneumococcal vaccine should in turn, be a useful routine management modality for children and adults with bronchiectasis. Indeed 5-yearly pneumococcal vaccination is recommended for patients with bronchiectasis (Chang 2002).

Pneumococcal vaccines are available in two major types; the older pneumococcal polysaccharide vaccine and the more recent pneumococcal conjugate vaccine. The 23-valent polysaccharide vac-

cine (PPV23) contains polysaccharide antigen from 23 serotypes and vaccine efficacy against invasive disease is estimated at 38-53% (Conaty 2004). Although clinical trials in younger adults have generally shown efficacy against pneumococcal pneumonia and, or bacteraemia, the trial evidence in the elderly is less robust (Honkanen 1999). Effectiveness in case-control studies generally range from 56-81% except Forrester et al who demonstrated no effectiveness (Forrester 1987). The PPV23 vaccine is relatively ineffective in young children aged under 2 years (Lee 2003). The heptavalent pneumococcal conjugated vaccine (PCV7) is directed against seven serotypes and recommended for use in children less than 5 years of age (McEllistrem 2005). Universal childhood vaccination in the United States has resulted in 70% decrease in invasive pneumococcal disease (IPD) in children <2 years and indirectly, contributed to prevention of adult IPD (Lexau 2005). The possibility of replacement serotype disease mandates continued data surveillance (McEllistrem 2005). Vaccines also incur cost and can result in adverse reactions, mostly occurring as local pain and swelling (Walker 2005, Jackson 2006). A review on the efficacy of pneumococcal vaccines for bronchiectasis will help guide clinical practice.

Efficacy of pneumococcal vaccines for other chronic respiratory diseases (Sheikh 2002, Granger 2006) and otitis media (Straetemans 2004) are covered in other Cochrane reviews. This systematic review will evaluate the evidence of efficacy of pneumococcal vaccination in children and adults with bronchiectasis.

OBJECTIVES

To evaluate the effectiveness of pneumococcal 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 pneumococcal vaccine in patients with bronchiectasis.

Types of participants

Adults or children with bronchiectasis (defined clinically or radiologically).

Exclusion criteria: Participants with other diseases where bronchiectasis is not present.

Types of interventions

All randomised controlled trials that utilised pneumococcal vaccine on children and adults with bronchiectasis. All types of pneumococcal vaccines were included.

Types of outcome measures

Attempts were made to obtain data on at least one of the following outcome measures:

- (A) for short term effectiveness (12 months or less)
 - a) proportions of participants who had respiratory exacerbations
 - b) proportions of participants who were hospitalised,
 - c) total numbers of days with respiratory symptoms
 - d) total number of hospitalised days
 - e) mean difference in bronchiectasis severity control (QOL, cough diary, Likert scale, visual analogue scale, level of interference of cough, cough diary, etc),
 - f) proportions experiencing adverse effects of the intervention, (e.g. local reaction, exacerbation immediately post vaccination, systemic effects (myalgia, fever, fatigue), etc)
- Outcomes (a) to (e) will be examined globally as well as also specifically to proven pneumococcal infections (from airway specimens or rising titres)
- (B) for medium to long term outcomes (more than 1 year)
 - g) radiology scores (high resolution computed tomography scans or chest radiograph)
 - h) lung function
 - i) bronchiectasis severity control (QOL, cough diary, Likert scale, visual analogue scale, level of interference of cough, cough diary, etc),
 - j) relevant airway markers of inflammation.
 - k) other non-respiratory outcomes (otitis media, bacteraemia, meningitis, etc) caused by pneumococcus.

Search methods for identification of studies

The following topic search strategy was used to identify relevant randomised controlled trials from electronic databases:

("bronchiectasis" OR "suppurative lung disease") AND ((vaccin* OR immunis*) AND (pneum*)) (all as textword or index terms).

For the full strategies see [Table 1](#)

Trials were identified from the following sources:

1. The Cochrane Airways Group Specialised Trials Register
2. The Cochrane Central Register of Controlled Trials (CENTRAL)
3. MEDLINE (1966 to Nov 2007). Topic search strategy combined with the RCT search filter as outlined in the Airways Group module.
4. OLDMEDLINE (1950 to 1965). Topic search strategy combined with the RCT search filter as outlined in the Airways Group module.

5. EMBASE (1980 to Nov 2007). 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.
7. Pharmaceutical companies that manufacture pneumococcal vaccines.

Data collection and analysis

Retrieval of studies: From the title, abstract, or descriptors, two reviewers (CC, AC) 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 adjudication (RS and PM).

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

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 odds 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. 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 2003). 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 pneumococcal 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) variation in the inclusion criteria;
- c) differences in the medications used in the intervention and comparison groups;
- d) differences in outcome measures;
- e) analysis using random effects model;
- f) analysis by "treatment received"; and
- g) analysis by "intention-to-treat".

RESULTS

Description of studies

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

The searches identified 3 potentially relevant publications but none fulfilled the study eligibility criteria (see Table of excluded studies).

Risk of bias in included studies

Not applicable as there were no eligible studies.

Effects of interventions

The Airways Group specialised register/search identified 44 potentially relevant titles. After assessing the abstracts, 3 publications were considered for inclusion into review including one non-English article (Russian). No additional studies were found in the review articles. No additional data were available from the two pharmaceutical companies contacted (Merck Sharp & Dohme and Wyeth in Australia). The only study in patients with bronchiectasis where a comparative group was used, was a non-randomised study in Russian ([Ryzhov 2005](#)). In this study ([Ryzhov 2005](#)) in children with chronic lung disease (including bronchiectasis), 25 were vaccinated with PPV23, 13 with Haemophilus influenzae vaccine and 40 children were not vaccinated. The authors described that, a year after vaccination with PPV23, *S. pneumoniae* were isolated in monoculture in 3 out of 25 cases (88% elimination) ([Ryzhov 2005](#)). An update search run in November 2007 did not identify any additional studies.

DISCUSSION

No randomised controlled trials comparing the effectiveness of pneumococcal vaccine as routine management in children and adults with bronchiectasis were identified.

In the target group examined in this Cochrane review, the one controlled study identified was not randomised ([Ryzhov 2005](#)); this study described efficacy with respect to microbiology of the sputum but clinical evaluation was not examined.

Large trials and meta-analysis have demonstrated that pneumococcal vaccination protects children and adults from invasive pneumococcal disease ([de Roux 2005](#)), thus many recommendations exist for regular pneumococcal vaccination for those at risk (including patients with suppurative lung disease). This Cochrane review however illustrates the glaring lack of evidence to support or refute these recommendations in the target group of people with bronchiectasis. Whilst we cannot always “wait for perfect data”, others have cautioned against “availability creep” with respect to the gap between policy and evidence ([Jefferson 2006](#)).

Until RCTs are undertaken to examine the question, we cannot be confident whether routine pneumococcal vaccination in children and adults with bronchiectasis is beneficial. The feasibility of performing RCTs in this target group is in question. For now, as children and adults with bronchiectasis are at increased risk for pneumonia and pneumococcal disease and there is some evidence that pneumococcal vaccine can reduce pneumonia and invasive pneumococcal disease ([Lucero 2004](#)), it would be prudent that providers follow guidelines from the national bodies such as Advisory Committee on Immunization Practices (in USA) ([ACIP](#)) and NIPS (Australia) ([NIPS](#)) regarding recommendations for pneumococcal vaccination of persons with bronchiectasis.

AUTHORS' CONCLUSIONS

Implications for practice

There is a lack of evidence for or against, routine additional pneumococcal vaccination for children and adults with bronchiectasis specifically. Circumstantial data suggests that pneumococcal vaccination is beneficial. As children and adults with bronchiectasis are at increased risk for pneumonia and pneumococcal disease and there is evidence that pneumococcal vaccine can reduce pneumonia and invasive pneumococcal disease, it would be prudent that providers follow national guidelines regarding recommendations for pneumococcal vaccination of persons with bronchiectasis. Individual risk factors for adverse events should be taken into account.

Implications for research

Randomised controlled trials to establish the efficacy of pneumococcal vaccination in reducing severity and frequency of respiratory exacerbations and pulmonary decline

in people with bronchiectasis are needed. As vaccine response alters with age, age-based cohorts should include young children (less than 2 years), children, adults and older adults. Various vaccine types and microbiological surveillance for possible serotype replacement should also be examined in these RCTs. However the difficulty in performing a RCT in the target group is acknowledged.

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Ryzhov 2005 *{published data only}*

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van Kessel 2005 *{published data only}*

van Kessel DA, van Velzen-Blad H, van den Bosch JM, Rijkers GT. Impaired pneumococcal antibody response in bronchiectasis of unknown aetiology. *European Respiratory Journal* 2005;**25**(3):482–9.

Vendrell 2005 *{published data only}*

Vendrell M, De Gracia J, Rodrigo MJ, Cruz MJ, Alvarez A, Garcia M, et al. Antibody production deficiency with normal IgG levels in bronchiectasis of unknown etiology. *Chest* 2005;**127**(1):197–204.

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Forrester 1987

Forrester HL, Jahnigen DW, LaForce FM. Inefficacy of pneumococcal vaccine in a high-risk population.. *American Journal of Medicine* 1987;**83**(3):425–30.

Granger 2006

Granger R, Walters J, Poole PJ, Lasserson TJ, Mangtani P, Cates CJ, et al. Injectable vaccines for preventing pneumococcal infection in patients with chronic obstructive pulmonary disease (Cochrane Review). *Cochrane Database of Systematic Reviews* 2006, Issue 4. [Art. No.: CD001390. DOI: 10.1002/14651858.CD001390.pub2]

Gursel 2006

Gursel G. Does coexistence with bronchiectasis influence intensive care unit outcome in patients with chronic obstructive pulmonary disease?. *Heart Lung* 2006;**35**(1):58–65.

Honkanen 1999

Honkanen PO, Keistinen T, Miettinen L, Herva E, Sankilampi U, Laara E, et al. Incremental effectiveness of pneumococcal vaccine on simultaneously administered influenza vaccine in preventing pneumonia and pneumococcal pneumonia among persons aged 65 years or older. *Vaccine* 1999;**17**(20-21):2493–500.

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Jefferson 2006

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Karadag 2005

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Singleton 2000

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Straetemans 2004

Straetemans M, Sanders EAM, Veenhoven RH, Schilder AGM, Damoiseaux RAMJ, Zielhuis GA. Pneumococcal vaccines for preventing otitis media (Cochrane Review). *Cochrane Database of Systematic Reviews* 2004, Issue 1. [Art. No.: CD001480. DOI: 10.1002/14651858.CD001480.pub2. Art. No.: CD001480. DOI: 10.1002/14651858.CD001480.pub2]

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Walker 2005

Walker FJ, Singleton RJ, Bulkow LR, Strikas RA, Butler JC. Reactions after 3 or more doses of pneumococcal polysaccharide vaccine in adults in Alaska. *Clinical Infectious Diseases* 2005;**40**(12):1730–5.

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Study	Reason for exclusion
Ryzhov 2005	Non RCT. This study in Russian was a comparative study in 40 controls (unvaccinated) and 25 children with chronic lung disease (including bronchiectasis) using Pneumovax 23. Hib vaccination was examined in another group
van Kessel 2005	Non RCT. Study examined antibody response to polysaccharide pneumococcal vaccine in 26 patients with bronchiectasis of unknown aetiology
Vendrell 2005	Non RCT. Study examined antibody response to a pneumococcal unconjugate vaccine and an Haemophilus influenzae type b conjugate vaccine in all consecutive adult patients with bronchiectasis of unknown etiology

DATA AND ANALYSES

This review has no analyses.

ADDITIONAL TABLES

Table 1. Search Strategies

Database	Search keywords
AIRWAYS REGISTER	("bronchiectasis" OR "suppurative lung disease") AND ((vaccin* OR immunis*) AND (pneum*)) (all as textword or index terms)
CENTRAL	#1 MeSH descriptor Bronchiectasis explode all trees #2 bronchiect* #3 suppurativ* near lung* #4 MeSH descriptor Ciliary Motility Disorders explode all trees #5 ciliary near dyskinesia #6 kartagener* #7 (#1 OR #2 OR #3 OR #4 OR #5 OR #6) #8 MeSH descriptor Pneumococcal Infections explode all trees #9 pneum* #10 MeSH descriptor Immunization explode all trees #11 MeSH descriptor Vaccines explode all trees #12 immuni* #13 vaccinat* #14 (#8 OR #9) #15 (#10 OR #11 OR #12 OR #13) #16 (#14 AND #15) #17(#16 AND #7)
MEDLINE (1966 to present) and OLDMEDLINE (1950 to 65) (Combined with RCT filter)	1. exp Bronchiectasis/ 2. bronchiect\$.mp. 3. (bronch\$ adj5 dilat\$).mp. 4. (suppurativ\$ adj5 lung\$).mp. 5. (ciliary adj3 dyskinesia).mp. 6. kartagener\$.mp. 7. or/1-6 8. exp Pneumococcal Infections/ 9. pneum\$.mp. 10. exp Immunization/ 11. exp Vaccines/ 12. vaccinat\$.mp. 13. immuni\$.mp. 14. (or/8-9) and (or/10-13) 15. (pneumoc\$ adj5 vaccin\$).mp. 16. (pneumoc\$ adj5 immuni\$).mp. 17. pneumococcal vaccines/ 18. or/14-17 19. 18 and 7

Table 1. Search Strategies (Continued)

EMBASE (1980 to 2006 Week 41) (Combined with RCT filter)	<ol style="list-style-type: none"> 1. exp Bronchiectasis/ 2. bronchiect\$.mp. 3. (bronch\$ adj5 dilat\$).mp. 4. (suppurativ\$ adj5 lung\$).mp. 5. (ciliary adj3 dyskinesia).mp. 6. kartagener\$.mp. 7. or/1-6 8. exp Pneumococcal Infections/ 9. pneum\$.mp. 10. exp Immunization/ 11. exp Vaccines/ 12. vaccinat\$.mp. 13. immuni\$.mp. 14. (or/8-9) and (or/10-13) 15. (pneumoc\$ adj5 vaccin\$).mp. 16. (pneumoc\$ adj5 immuni\$).mp. 17. pneumococcal vaccines/ 18. or/14-17 19. 18 and 7
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WHAT'S NEW

Last assessed as up-to-date: 19 November 2007.

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

HISTORY

Protocol first published: Issue 1, 2007

Review first published: Issue 2, 2007

Date	Event	Description
10 December 2006	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

For the protocol: Protocol was written by both CC and AC. RS reviewed the protocol. For the review: CC and AC selected articles from search, extracted data and wrote the review. RS and PM contributed to writing the review and would have been adjudicators if disagreements had occurred.

DECLARATIONS OF INTEREST

None declared.

SOURCES OF SUPPORT

Internal sources

- Royal Children's Hospital Foundation, Brisbane, Australia.

External sources

- National Health and Medical Research Council, Australia.

INDEX TERMS

Medical Subject Headings (MeSH)

Bronchiectasis [*complications]; Pneumococcal Infections [*prevention & control]; Pneumococcal Vaccines [*therapeutic use]

MeSH check words

Adult; Child; Humans