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Pneumococcal vaccines for cystic fibrosis (Review)

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[Intervention Review]

Pneumococcal vaccines for cystic fibrosis

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ABSTRACT

Background

Invasive pneumococcal disease is associated with significant mortality and many countries have introduced routine pneumococcal vaccination into their childhood immunisation programmes. Whilst pneumococcal disease in cystic fibrosis is uncommon, pneumococcal immunisation may offer some protection against pulmonary exacerbations caused by this pathogen. In the USA and UK pneumococcal vaccination is currently recommended for all children and adults with cystic fibrosis. This is an update of a previously published review.

Objectives

To assess the efficacy of pneumococcal vaccines in reducing morbidity in people with cystic fibrosis.

Search methods

We searched the Cochrane Cystic Fibrosis and Genetic Disorders Group Cystic Fibrosis Trials Register, which comprises references identified from comprehensive electronic database searches and handsearches of relevant journals and abstract books of conference proceedings. In addition, the pharmaceutical manufacturers of the polysaccharide and conjugate pneumococcal vaccines were approached.

Date of the most recent search: 27 June 2016.

Selection criteria

Randomised and quasi-randomised controlled trials comparing pneumococcal vaccination (with either a polysaccharide or conjugate pneumococcal vaccine) with non-vaccination or placebo in children or adults with cystic fibrosis were eligible for inclusion.

Data collection and analysis

No relevant trials were identified.

Main results

There are no trials included in this review.

Authors' conclusions

As no trials were identified we cannot draw conclusions on the efficacy of routine pneumococcal immunisation in people with cystic fibrosis in reducing their morbidity or mortality. As many countries now include pneumococcal immunisation in their routine childhood vaccination schedule it is unlikely that future randomised controlled trials will be initiated. Rigorously conducted epidemiological studies may offer the opportunity to evaluate the efficacy of pneumococcal vaccination in reducing morbidity and mortality in people with cystic fibrosis.

PLAIN LANGUAGE SUMMARY

Pneumococcal vaccines for children and adults with cystic fibrosis

Review question

We reviewed the evidence about the effect of vaccinating people with cystic fibrosis against infection with pneumococcal bacteria.

Background

Cystic fibrosis is an inherited disease which causes mucus in the lungs to be more sticky than normal, leading to frequent lung infections and lung damage. Pneumococcus is a type of bacteria that can cause infection throughout the body. These infections can be very serious and may lead to severe illness and death.

There are two types of vaccine that can help protect people against some forms of pneumococcus bacteria. One vaccine is used in children under two years of age and the second is used in older children and adults. This review aimed to find trials that compared vaccinations (either vaccine) to no vaccination or a vaccination with a placebo (dummy drug) to work out whether vaccinating against pneumococcus bacteria can reduce serious illness and death in people with cystic fibrosis. This is an update of a previously published review.

Search date

Evidence is current to 27 June 2016.

Study characteristics

We did not find any relevant trials to include in this review.

Key results

The evidence to support the routine use of vaccines against pneumococcal infection is not strong; however, many countries now recommend that all children receive the vaccine as part of their childhood immunisation programmes.

BACKGROUND

Description of the condition

Cystic fibrosis (CF) is one of the most common life-threatening conditions, with over 9000 affected people in the UK ([UK Cystic Fibrosis Trust 2012](#)). It is caused by the inheritance of two mutated copies of a gene coding for the cystic fibrosis transmembrane conductance regulator protein, with 1 in 25 Caucasian people in the UK being carriers of a mutated gene ([UK Cystic Fibrosis Trust 2012](#)). The incidence of CF varies worldwide with 1 in 2000 to 3000 newborns affected in Europe, 1 in 3500 in North America, 1 in 3900 to 7500 in South America, 1 in 15,000 in the Middle East and 1 in 40,000 to 350,000 in Asia ([Collazo 1995](#); [Dodge 2007](#); [Frossard 1998](#); [Kosorok 1996](#); [Powers 1996](#); [Raskin 2008](#); [Yamashiro 1997](#)). In CF, a multisystem disorder, the abnormal protein results in the production of thickened mucus, with significant respiratory and gastrointestinal manifestations. Life expectancy has increased dramatically for people with CF over the past 20 years and a baby born in 2010 can expect to live until their fifth decade ([Dodge 2007](#)).

Pulmonary exacerbations in CF are widely acknowledged to contribute to an acceleration in the decline of respiratory function in addition to the increase in symptoms during the exacerbation ([Rosenbluth 2004](#); [Sanders 2010](#)). However, non-pulmonary invasive pneumococcal disease can also have an adverse effect on CF disease by contributing to sub-optimal nutrition, decreased mobility, and in certain cases the need for mechanical ventilation. Pulmonary exacerbations in CF are most frequently associated with *Staphylococcus aureus*, *Haemophilus influenzae* and *Pseudomonas aeruginosa* (*P. aeruginosa*) ([Goss 2007](#)). *Streptococcus pneumoniae* (*S. pneumoniae*) was found to be the fourth most common bacterial organism isolated from the sputa of people with CF in a study from the 1970s; however, a more recent study in the USA found only 3.4% of people with CF were colonised with *S. pneumoniae* and its growth was infrequently associated with pulmonary exacerbations ([Burns 1998](#); [Høiby 1974](#); [Lahiri 2001](#)).

Invasive pneumococcal disease is usually defined as isolation of *S. pneumoniae* from a normally sterile site and thus includes meningitis, septicaemia and pneumonia. Invasive pneumococcal disease is serious and every year in England and Wales 5000 to 6000 cases are reported to the Health Protection Agency (HPA) ([Health Protection Agency 2010](#)). A 30-year population-based cohort study of children and adults in Denmark found an overall 30-day mortality rate of 18% following invasive pneumococcal disease, with mortality being significantly associated with high comorbidity level ([Harboe 2009](#)). A 20-year surveillance in Nottingham (UK) found 11% mortality in children with invasive pneumococcal disease, with a higher mortality of 23% in those with a pre-existing underlying condition ([Ispahani 2004](#)). Worldwide, pneumococcal disease is estimated to be responsible for more than one third of the two million global annual child deaths due to acute respiratory infections ([Williams 2002](#)).

Description of the intervention

Whilst invasive pneumococcal disease in CF is uncommon, pneumococcal immunisation may offer some protection against exacerbations with this pathogen. A study measuring serum precipitins to bacterial pathogens in children with CF found 4% had serum precipitins to *S. pneumoniae* ([May 1972](#)). Vaccination

with the pneumococcal polysaccharide vaccine (PPV), which provides protection against 23 serotypes of pneumococcus, is recommended in the UK for all adults over 65 years of age and for all children and adults (aged 2 to 64 years) who are considered high risk, for example, due to a chronic illness such as CF ([National Health Service 2010](#)). The HPA states that the PPV covers 96% of the pneumococcal serotypes that cause invasive pneumococcal disease in the UK. The pneumococcal conjugate vaccine (PCV) is recommended in the UK for all children who are under the age of two years, as part of the routine childhood immunisation schedule ([National Health Service 2010](#)). The currently used conjugate vaccine protects against 13 serotypes of pneumococcus. In the USA, it is currently recommended for all people with CF to have pneumococcal vaccination ([Kroger 2006](#)).

How the intervention might work

An observational study of patients with CF in 2001 reported pre-vaccination anti-pneumococcal antibody levels, measured by enzyme-linked immunosorbent assay (ELISA), as protective in the majority of people with CF ([Lahiri 2001](#)). However, they also found that 17% to 39% did not have adequate protective levels and hence reiterated the current recommendation in the USA for all people with CF to have pneumococcal vaccination. Vaccination with either a polysaccharide or conjugate pneumococcal vaccine aims to reduce the burden of morbidity and mortality that is associated with invasive pneumococcal disease. The immunisation should provide protection against the pneumococcal serotypes covered by the particular vaccine; however, there are over 90 known serotypes and concerns that replacement will occur with the non-vaccine serotypes becoming more prevalent have already been realised in the UK ([Health Protection Agency 2010](#); [Pletz 2008](#)).

Why it is important to do this review

This review aims to establish whether pneumococcal vaccines reduce the morbidity associated with invasive pneumococcal disease in people with CF. Immunisation against pneumococcus has become increasingly prevalent in the past decade and is now included as part of the routine immunisation schedule for children in the UK. Children with chronic diseases have a 1.4-fold increased risk of invasive pneumococcal disease compared to healthy children ([Hjuler 2008](#)); and yet a recent study in Italy found low uptake rates of pneumococcal vaccination of less than 20% amongst children with CF, with the authors speculating this may be due to a lack of awareness of the severity of pneumococcal disease ([Giannattasio 2010](#)). There has been recent controversy regarding the efficacy of the polysaccharide vaccine, particularly regarding re-vaccination, which is recommended every five years ([Pletz 2008](#)). Although serious adverse vaccine reactions are rare it is important to establish the efficacy of the vaccines in reducing the burden of pneumococcal disease in people with CF and to date there are no systematic reviews on pneumococcal vaccines for people with CF. The results of this review may aid in increasing the uptake of pneumococcal vaccine in people with CF in countries where it is not included in routine vaccination schedules or guide inclusion of this vaccine into standard childhood immunisation programmes in such countries.

This version of the review is an update of previously published versions ([Burgess 2012](#); [Burgess 2014](#)).

OBJECTIVES

To assess the efficacy of pneumococcal vaccines in reducing morbidity in people with CF.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised and quasi-randomised controlled trials were eligible for inclusion.

Types of participants

Children and adults with CF, diagnosed on the basis of sweat testing or genotype.

Types of interventions

Vaccination with either a polysaccharide or conjugate pneumococcal vaccine compared with non-vaccination or placebo.

Types of outcome measures

Primary outcomes

1. Quality of life (validated scores e.g. Cystic Fibrosis Questionnaire-Revised version (CFQ-R) (Quittner 2009) and Cystic Fibrosis Quality of Life Questionnaire (CFQoL) (Gee 2000)).
2. Exacerbation of respiratory disease over the period of the study
 - a. pulmonary exacerbation (as defined in trial protocol)
 - b. need for hospitalisation
 - c. need for additional antibiotic therapy
 - i. oral
 - ii. intravenous
3. Infection with pneumococcus (invasive pneumococcal disease of vaccine-specific serotype)

Secondary outcomes

1. Adverse vaccine reaction
2. Respiratory function as assessed by spirometric measures
 - a. forced expiratory volume in one second (FEV₁)
 - b. forced vital capacity (FVC)
3. Survival
4. Functional antibody levels against pneumococcus (assessed by ELISA for polysaccharide vaccine and serotype-specific immunoassay for conjugate vaccine)
5. Radiographic appearances
 - a. chest radiograph appearances
 - b. chest CT scan appearances
6. Emergence of other pathogens
 - a. *P. aeruginosa*
 - b. *Nontuberculous mycobacterium*
 - c. *Staphylococcus* (including MRSA)
 - d. non-vaccine pneumococcal serotypes (serotype replacement)
 - e. other

Search methods for identification of studies

Electronic searches

We aimed to identify relevant studies from the Group's Cystic Fibrosis Trials Register using the terms: 'streptococcus pneumoniae [pneumococcus]' AND 'vaccine'.

The Cystic Fibrosis Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated each new issue of *The Cochrane Library*), weekly searches of MEDLINE, a search of Embase to 1995 and the prospective handsearching of two journals - *Pediatric Pulmonology* and the *Journal of Cystic Fibrosis*. Unpublished work is identified by searching the abstract books of three major cystic fibrosis conferences: the International Cystic Fibrosis Conference; the European Cystic Fibrosis Conference and the North American Cystic Fibrosis Conference. For full details of all searching activities for the register, please see the relevant sections of the [Cochrane Cystic Fibrosis and Genetic Disorders Group Module](#).

Date of the latest search: 27 June 2016.

Searching other resources

The manufacturers of the pneumococcal vaccines were contacted for information on randomised or quasi-randomised controlled trials involving their vaccines. It was planned to hand-search references of any identified studies for references to additional relevant studies.

Data collection and analysis

The search did not identify any studies and therefore the processes detailed below were not undertaken, but the authors intend to follow these steps if they identify any studies in future searches.

Selection of studies

Both authors plan to independently select the studies for inclusion in the review. They plan to examine the titles and abstracts of publications identified by the search in order to exclude those studies which do not meet the inclusion criteria. The authors will examine the full texts of all remaining reports to assess eligibility for inclusion in the review. They intend to resolve any disagreements on those studies to be included by discussion and consensus or the advice of the Contact Editor, if necessary.

Data extraction and management

Both authors will independently extract data from the eligible studies using a customised data collection form and compare forms to ensure consistency of interpretation. Where discrepancies arise, the authors intend to discuss these and reach consensus or seek advice from the review's Contact Editor. The authors plan to use the extracted data to populate the 'Characteristics of included studies' table in Review Manager (RevMan 2014).

The authors plan to extract the following data:

- study design;
- CF diagnostic criteria;
- participants;
- generation of allocation sequence;
- allocation concealment;

- blinding;
- type of pneumococcal vaccine;
- comparison intervention;
- outcomes, as detailed in the [Types of outcome measures](#) section of this review (primary outcomes and secondary outcomes);
- funding source.

Assessment of risk of bias in included studies

The authors intend to assess the risk of bias using the 'Risk of bias' assessment tool as documented in section 8.5 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). They plan to assess the following domains as having a low risk of bias, a high risk of bias or an unclear risk of bias:

1. sequence generation;
2. allocation concealment;
3. blinding (of participants, personnel and outcome assessors);
4. incomplete outcome data;
5. selective outcome reporting;
6. other sources of bias.

The authors plan to display the results of the risk of bias assessment in the 'Risk of bias' table.

Measures of treatment effect

The authors plan to perform a meta-analysis for the outcomes of interest from any studies eligible for inclusion in the systematic review. They plan to analyse dichotomous data by calculating the odds ratio (OR) and 95% confidence intervals (CIs), if appropriate. They aim to analyse continuous data using the mean difference (MD) from baseline, or mean post-intervention values, for the intervention and comparator groups, with standard deviations (SD) for each group. They plan to calculate pooled estimates of treatment effects across the included studies using pooled OR for dichotomous data and pooled MDs for continuous data and the corresponding 95% CIs. If possible, the authors plan to calculate the numbers needed to treat (NNT) and their 95% CIs from the pooled OR and its 95% CI for a specific baseline risk, which is the sum of all the events in the control groups (in all studies) divided by the total participant numbers in control groups in all studies. They intend to do this using an online calculator ([Cates 2003](#)).

Unit of analysis issues

As this review is assessing vaccine efficacy cross-over studies are not appropriate. If any cluster-randomised studies are eligible for inclusion, then the authors plan to analyse these as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Deeks 2011](#)).

Dealing with missing data

If the authors identify any study with incomplete or missing data, they intend to contact the study's principle investigator for clarification or further information.

Assessment of heterogeneity

The authors intend to describe any heterogeneity between the included studies and assess this using the standard Chi² test. They will also consider the I² statistic, which describes the percentage of variability in effect estimates that is due to heterogeneity

rather than sampling error ([Higgins 2003](#)). The authors plan to base their interpretation of the I² statistic for this review on the guidance for thresholds detailed in the *Cochrane Handbook for Systematic Reviews of Interventions*, such that they will regard below 50% as low heterogeneity, between 50% and 75% as moderate heterogeneity and over 75% as high heterogeneity ([Deeks 2011](#)).

Assessment of reporting biases

The authors plan to assess reporting bias by comparing study protocols (as detailed on the clinical trials register) with the published results of the study to examine for selective reporting. If they are able to include an adequate number of studies in the review (at least 10), then they plan to construct a funnel plot and consider publication bias. If they obtain an asymmetrical funnel plot, they intend to explore alternative causes in addition to publication bias.

Data synthesis

The authors plan to analyse any data using a fixed-effect model, unless there is evidence of significant heterogeneity between the included studies, in which case they will use a random-effects model.

Subgroup analysis and investigation of heterogeneity

If the authors identify at least 10 studies they plan to undertake subgroup analyses on the following:

1. type of vaccine;
2. type of invasive pneumococcal disease, e.g. pneumococcal pneumonia, pneumococcal meningitis, etc.;
3. vaccine versus non-vaccine serotype of pneumococcal disease;
4. age at vaccination;
5. primary vaccination versus re-vaccination.

Sensitivity analysis

If the authors find an adequate number of studies, they plan to perform a sensitivity analysis based on the risk of bias, i.e. they will analyse data with and without studies deemed to be of high risk of bias.

RESULTS

Description of studies

Results of the search

No studies were identified for this review.

Risk of bias in included studies

No studies were identified for this review.

Effects of interventions

No studies were identified for this review.

DISCUSSION

This review aimed to assess the efficacy of pneumococcal vaccines in reducing morbidity in people with CF, but there were no eligible studies identified in the search. Whilst recognising that

invasive pneumococcal disease in people with CF is uncommon, a significant proportion of this population do not have adequate protective pre-vaccination anti-pneumococcal antibody levels and for these individuals vaccination may prevent a pneumococcal pneumonia (Lahiri 2001). In addition to the decline in lung function associated with pulmonary exacerbations in people with CF, the serious morbidity associated with non-pulmonary invasive pneumococcal disease would likely contribute to a decline in their general health. It is surprising that no studies were identified evaluating the efficacy of pneumococcal vaccine in people with CF. The emergence of routine childhood immunisation against pneumococcus in many countries makes it unlikely that any new randomised or quasi-randomised controlled studies will be conducted in early childhood. Future opportunities for evaluation of the efficacy and safety of pneumococcal vaccine use in people with CF may be limited to assessing the use of repeated vaccination. There is no current data on the timing of revaccination and papers addressing the subject of repeat vaccination generally advise to follow national guidelines (Jain 2009; Malfroot 2005). Measuring antibody titres against the various pneumococcal vaccine serotypes at certain time-points following vaccination could aid in deciding when to revaccinate individuals.

Agreements and disagreements with other studies or reviews

A Cochrane review assessing the effectiveness of pneumococcal vaccine in people with bronchiectasis, which is also a chronic suppurative lung disease, concluded that there was limited evidence to support the routine use of pneumococcal vaccine in adults with chronic lung disease and no data on the efficacy of pneumococcal vaccine on pulmonary decline or on how often the vaccination should be repeated (Chang 2009). Due to this lack of evidence they recommended health care providers should follow national guidelines on vaccination schedules.

AUTHORS' CONCLUSIONS

Implications for practice

There is a lack of evidence to support the use of pneumococcal vaccines in people with CF; however, in many countries routine pneumococcal vaccination is emerging as part of national vaccination programmes and it is recommended that people with CF receive pneumococcal vaccination as part of standard immunisations. However, in countries where pneumococcal vaccination is not included in the national programme, there is insufficient evidence to recommend it in people with CF.

Implications for research

As pneumococcal vaccination has become part of many national immunisation schedules, it is unlikely that randomised controlled studies in CF patients will be initiated. This lack of evidence-base for efficacy has hampered the universal provision of pneumococcal vaccination to people with CF in countries where it is not included in the national schedule. Other study designs, such as rigorously conducted epidemiological studies, may provide some evidence to assess the efficacy of these vaccines in reducing morbidity and mortality in people with CF. Such studies are at a risk of bias and the quality of design, conduct, analysis and reporting must be carefully considered to minimise potential bias. Future updates of this review will consider assessing non-randomised clinical studies.

ACKNOWLEDGEMENTS

We would like to thank the former Contact Editor for this review, Dr Heather Elphick, and Nikki Jahnke, a Managing Editor of the Cochrane Cystic Fibrosis and Genetic Disorders Group for their helpful comments throughout the development of the protocol and review.

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WHAT'S NEW

Date	Event	Description
8 April 2021	Review declared as stable	Due to a lack of research in this area the Editorial Board of the Cystic Fibrosis and Genetic Disorders Review Group have decided to no longer update this review.

HISTORY

Protocol first published: Issue 12, 2010

Review first published: Issue 9, 2012

RevMan 2014 [Computer program]

The Nordic Cochrane Centre, The Cochrane Collaboration Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

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Date	Event	Description
1 September 2016	New citation required but conclusions have not changed	Since no new data have been added to the review at this update, our conclusions remain the same.
27 June 2016	New search has been performed	A search of the Cystic Fibrosis and Genetic Disorders Review Group's Cystic Fibrosis Trials Register did not identify any new references potentially eligible for inclusion in the review.
23 July 2014	New citation required but conclusions have not changed	No new references have been included in this updated review; our conclusions remain the same.
23 July 2014	New search has been performed	A search of the Cystic Fibrosis & Genetic Disorders Review Group's Cystic Fibrosis Trials Register did not identify any potentially eligible new references.

CONTRIBUTIONS OF AUTHORS

Kevin Southern conceived the protocol and both authors contributed to drafting the protocol and the review.

DECLARATIONS OF INTEREST

Laura Burgess declares no potential conflict of interest.

Kevin Southern declares no potential conflict of interest.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Institute for Health Research, UK

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INDEX TERMS

Medical Subject Headings (MeSH)

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

MeSH check words

Adult; Child; Humans