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Influenza vaccine for preventing acute otitis media in infants and children [Protocol]

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Influenza vaccine for preventing acute otitis media in infants and children (Protocol)

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:
To assess the effects of influenza vaccination, compared to no vaccination, on the occurrence of acute otitis media in infants and young children.

BACKGROUND

Acute otitis media (AOM) is one of the most common infections of childhood and is a leading cause of physician office visits and antibiotic prescribing for children in developed countries (Charles 2004; Freid 1998). AOM is characterised by the rapid onset of symptoms and signs of acute infection of the middle ear, such as ear pain, diminished hearing, fever, irritability and inflammation of the eardrum. Apart from the distress caused by the symptoms of AOM to the child and parents or carers, the costs of office visits, treatment and days lost from work by carers are significant.

The acute infection usually resolves within days. However, fluid may persist in the middle ear and impair hearing for several months after AOM. The presence of fluid in the middle ear in the absence of acute signs and symptoms is called otitis media with effusion (OME). Some children are prone to repeated episodes of AOM; US studies indicate that approximately 20% of children have recurrent AOM (Daly 1999; Teele 1989). There are concerns that the hearing impairment associated with frequent or persistent middle ear inflammation in young children may adversely affect development of language and communication skills.

In some cases, AOM progresses to chronic suppurative otitis media (CSOM) where there is chronic infection, perforation of the eardrum, ear discharge and hearing impairment. CSOM is particularly prevalent in developing countries and high-risk groups in developed countries (such as Australian Aborigines), where it is a major contributor to hearing loss (Berman 1995; Couzos 2001). Serious complications of AOM, such as meningitis and intracranial abscess, are very rare in developed countries but contribute to significant mortality in the developing world; in 1993, otitis media was associated with the deaths of 51,000 children under five years of age in developing countries (World Bank 1993).

The incidence of AOM is greatest in children under two years of age with US data indicating that almost 40% of children have had at least one episode by the age of six months and more than 60% by 12 months (Daly 1999; Teele 1989). Risk factors for AOM include male gender, having older siblings, a family history of otitis media, attending daycare, lack of breast feeding, exposure to tobacco smoke and pacifier use (Duncan 1993; Niemela 1995; Rovers 2004; Stenstrom 1993; Uhari 1996).

Antibiotics have long been the mainstay of treatment. However, the modest benefit of antibiotics (Glasziou 2003) may not outweigh their risks. Many current guidelines advise against routine antibiotic treatment to limit adverse effects and the selection of resistant strains (Spicer 2003; SIGN 2003).

The shortcomings of antibiotic treatment have highlighted the importance of effective preventative strategies for AOM. Identifying and avoiding modifiable risk factors may help to prevent episodes of AOM. Prophylactic antibiotics have been used for recurrent AOM but it is not clear if the benefit of this strategy outweighs the potential harms (O’Neill 2004). The use of tympanostomy tubes is also controversial (O’Neill 2004). Cochrane reviews of prophylactic...
lactic antibiotics and tympanostomy tubes are planned (Langton Hewer 2004; Leach 2003).

Vaccination strategies for preventing AOM have been a focus of recent research. A Cochrane review concluded that currently available pneumococcal vaccines are minimally effective in preventing AOM (Straetemans 2004); vaccines against the two other major bacterial pathogens, Moraxella catarrhalis (M. catarrhalis) and non-typeable Haemophilus influenzae (H. influenzae) are in development (McMichael 2003).

Viral upper respiratory infections frequently precede the onset of AOM and, as reviewed by Heikkinen 2003, evidence for the role of respiratory viruses in the development of AOM is growing. Currently, influenza is the only respiratory virus for which vaccination is available. A number of studies have suggested that influenza vaccination might help to prevent AOM (Belshe 2000; Marchisio 2002) and vaccination has been proposed as a secondary prevention measure on this basis (Errasmoupe 2000). However, a recent large randomised controlled trial found no significant benefit from vaccination (Hoberman 2003). Given the burden of illness, the cost of managing AOM and the apparent conflict in the literature it is timely to examine the evidence in influenza vaccination for preventing AOM.

**OBJECTIVES**

To assess the effects of influenza vaccination, compared to no vaccination, on the occurrence of acute otitis media in infants and young children.

**CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW**

**Types of studies**

Randomised studies comparing influenza vaccine with placebo or no treatment. Studies may be blinded or open-label and may use either a placebo vaccine or no placebo. Studies without random or quasi-random allocation to treatment groups will be excluded.

**Types of participants**

Infants and children of either gender with or without a history of recurrent otitis media. Studies including participants aged over 18 years will be excluded.

**Types of intervention**

Vaccination with any influenza vaccine, live or inactivated, and whole, split virus or subunit-type vaccines. Vaccines may be monovalent or multivalent and given via any route of administration. Studies in which participants could receive other potentially preventative interventions will be excluded unless these interventions were equally accessible to both treatment groups.

**Types of outcome measures**

AOM must be diagnosed by a clinician using any diagnostic criteria. Studies in which diagnosis of AOM is based on participant or carer report alone will be excluded.

**Primary outcomes**

1. Number of patients having at least one episode of AOM during the 12 months following vaccination

2. Number of episodes of AOM recorded, adjusted for follow up

**Secondary outcomes**

1. Complications of otitis media (e.g. CSOM, mastoiditis, surgery)

2. Use of antibiotics to treat AOM or its complications

3. Time lost from daycare/school (for children) or from work (for parents or carers) due to AOM

4. Outcomes related to loss of hearing and its potential effects on language and learning

5. Effects on child or carer quality of life

6. Costs of managing AOM

We will also record the occurrence of vaccine-related adverse events in the randomised controlled trials used for our primary analysis. However, no statistical analysis will be applied to this information.

**SEARCH METHODS FOR IDENTIFICATION OF STUDIES**

See: Acute Respiratory Infections Group methods used in reviews.

We will search the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library latest issue) (which includes the Cochrane Acute Respiratory Infections Group’s specialised register), MEDLINE (1966 to present) and EMBASE (1990 to present).

The MEDLINE search will use the following keywords and MeSH terms in combination with the highly sensitive search strategy for identifying controlled trials as defined by the Cochrane Collaboration and detailed in Appendix 5b of the Cochrane Reviewers’ Handbook (Edition 4.2). A similar strategy will be used to search EMBASE and the CENTRAL. There will be no language restrictions on the search.

Otitis media/

AOM.mp

OM.mp

middle ear adj10 infection

Viral vaccines/

Influenza vaccine/

(influenza or flu) adj10 (vaccin$ or immun$)

As studies are identified, the search strategy will be amended to include any relevant index terms that have been overlooked. To
identify unpublished studies we will search the reference lists of identified studies and review articles. We will also contact experts in the field and pharmaceutical companies that market influenza vaccines. Clinical trial registers (such as clinicaltrials.gov and the UK National Research Register) will be searched for records of ongoing studies.

**Methods of the Review**

Two authors will independently assess study eligibility and methodological quality and extract and enter data as detailed below. Any disagreements will be resolved by discussion and consensus; a third reviewer will be consulted where disagreement cannot be resolved. Where information is missing from the study reports, or clarification is needed, we will contact the authors to request the required information.

**Assessment of study eligibility**

Initially we will scan the titles and abstracts from the searches and will obtain full text articles when a study appears to meet the eligibility criteria or when there is insufficient information in the abstract to assess eligibility. We will then use a standardised form to assess the eligibility of each study, based on the full article. When studies are excluded the reasons for exclusion will be documented.

**Assessment of study quality**

We will assess study quality using a standardised form based on the Jadad scale (Jadad 1996). Each study will be assigned a quality rating based on the scale: those with a score less than three are poor quality.

**Data extraction**

We will extract data using a form designed for the purpose. Information extracted will include:

- participant characteristics (age, sex, race, history of recurrent acute otitis media, attendance at day care or school);
- study setting;
- type of vaccine used;
- matching of vaccine with strains circulating at time of study;
- method for diagnosing AOM;
- occurrence of AOM and its complications during follow up period;
- use of antibiotics to treat AOM or its complications;
- time lost from daycare/school (for children) or from work (for parents or carers) due to AOM;
- outcomes related to loss of hearing and its potential effects on language and learning;
- effects on child or carer quality of life;
- costs of managing AOM;
- occurrence of possible vaccine-related adverse events during follow up.

**Statistical analysis**

Where studies report sufficiently similar outcomes we will perform a meta-analysis using Review Manager (RevMan). A fixed-effect model will be used initially. We will test for heterogeneity using the chi-squared test; outcomes with statistically significant heterogeneity (p value < 0.05) will be re-analysed using a random-effects model. For dichotomous outcomes we will report odds ratios. For continuous outcomes we will report weighted mean differences.

We will perform a sensitivity analysis of study quality by re-analysing the primary outcomes excluding poor quality studies.

The following factors will be explored as possible sources of heterogeneity. If adequate data are available, subgroup analyses will be based on these factors:

- age of children;
- presence or absence of a history of recurrent AOM;
- type and route of administration of vaccine;
- method and criteria used for diagnosing AOM (objective versus subjective);
- matching of vaccine with strains circulating at time of study;
- study setting (for example, indigenous versus non-indigenous, urban versus rural, socio-economic status, day care/school versus home care).

The primary outcome measures will be analysed by intention to treat, where possible. Where patient data are missing from the study report and unavailable from the investigators the primary analysis will be based on available cases. We will explore the impact of missing data on the primary outcomes in a sensitivity analysis using imputed outcomes.

**Potential Conflict of Interest**

None known.

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- No sources of support supplied

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Additional references

Belche 2000

Berman 1995

Charles 2004

Couzos 2001

Daly 1999

Duncan 1993

Errasmoupe 2000

Freid 1998

Glasziou 2003

Heikkinen 2003

Hoberman 2003

Jadad 1996

Langton Hewer 2004

Leach 2003

Marchisio 2002

McMichael 2003

Niemela 1995

O’Neill 2004

Rovers 2004

SIGN 2003

Spicer 2003

Stenstrom 1993

Straetemans 2004

Teelie 1989

Uhari 1996

World Bank 1993
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