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Vaccines for preventing influenza in people with cystic fibrosis (Review)

Dharmaraj P, Smyth RL

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[Intervention Review]

Vaccines for preventing influenza in people with cystic fibrosis

Poonam Dharmaraj[1], Rosalind L Smyth[2]

[1]Diabetes & Endocrinology, Alder Hey Children's NHS Foundation Trust, Liverpool, UK. [2]Institute of Child Health, UCL, London, UK

Contact address: Poonam Dharmaraj, poonamd@doctors.org.uk.

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ABSTRACT

Background

Viral respiratory tract infections in people with cystic fibrosis have a deteriorating effect on their lung function and disease progression. Annual influenza vaccination is therefore commonly recommended for people with cystic fibrosis.

Objectives

To assess the effectiveness of influenza vaccination for people with cystic fibrosis.

Search methods

We searched the Cochrane Cystic Fibrosis and Genetic Disorders Group Trials Register which comprises of references identified from comprehensive electronic database searches and handsearching of relevant journals and abstract books of conference proceedings. We also contacted the companies which market the influenza vaccines used in the trials to obtain further information about randomised controlled trials.

Date of the most recent search of the Cochrane Cystic Fibrosis and Genetic Disorders Group's Cystic Fibrosis Trials Register: 08 July 2013.

Selection criteria

All randomised and quasi-randomised trials (published or unpublished) comparing any influenza vaccine with a placebo or with another type of influenza vaccine.

Data collection and analysis

Two authors independently assessed study quality and extracted data. Additional information was obtained by contacting the investigators when it was indicated.

Main results

Four studies enrolling a total of 179 participants with cystic fibrosis (143 (80%) were children aged 1 to 16 years) were included in this review. There was no study comparing a vaccine to a placebo or a whole virus vaccine to a subunit or split virus vaccine. Two studies compared an intranasal applied live vaccine to an intramuscular inactivated vaccine and the other two studies compared a split virus to a subunit vaccine and a virosome to a subunit vaccine (all intramuscular). The incidence of all reported adverse events was high depending on the type of influenza vaccine. The total adverse event rate ranged from 48 out of 201 participants (24%) for the intranasal live vaccine to 13 out of 30 participants (43%) for the split virus vaccine. With the limitation of a statistical low power there was no significant difference between the study vaccinations. None of the events were severe. All study influenza vaccinations generated a satisfactory serological antibody response. No study reported other clinically important benefits.

Authors' conclusions

There is currently no evidence from randomised studies that influenza vaccine given to people with cystic fibrosis is of benefit to them. There remains a need for a well-constructed clinical study, that assesses the effectiveness of influenza vaccination on important clinical outcome measures.

PLAIN LANGUAGE SUMMARY

Vaccines for preventing influenza in people with cystic fibrosis

People with cystic fibrosis have blocked airways which results in frequent airway infections. Infections with viral diseases like influenza ("the flu") can worsen lung damage. Doctors therefore often advise people with cystic fibrosis to be vaccinated against influenza every year. We searched for studies which compared different vaccines or compared vaccination to placebo. We were able to include four studies with 179 people in the review. Most (143) were under 16 years old. No study compared one vaccine to placebo. There were a high number of drop outs in two of the studies. Vaccination does result in an immune system response to the types of influenza used in the vaccine. However, this response may not result in protection against influenza infection or lung damage. There were a high number of adverse events, but none were serious or persistent. There is no evidence to show if regular influenza vaccine benefits people with cystic fibrosis.

BACKGROUND

Description of the condition

Influenza is an acute viral infection affecting the respiratory tract and can cause death in susceptible individuals, especially the elderly, with figures as high as 3000 to 4000 per year in Great Britain (Ashley 1991). Immunisation is therefore recommended to people with an underlying disease, e.g. a chronic respiratory, heart or renal disease, diabetes mellitus or an immunodeficiency, in the elderly population (aged 65 years and older) and in those living in nursing or residential homes (HMSO 1996).

Respiratory exacerbations, generally thought to be caused by bacterial infections are responsible for considerable morbidity and mortality in people with CF and are treated with oral or intravenous antibiotics.

Observational studies have suggested an adverse outcome in terms of lung function and disease progress in people with CF following infection with Influenza A virus and other viral respiratory tract infections (Collinson 1996; Conway 1992; Ferson 1991; Petersen 1981; Ramsey 1989; Ryan 1997; Smyth 1995; Wang 1984) and there are suggestions that a further indirect effect plays a role. A cohort study in 300 Danish people with CF found that the majority contracted their first colonisation and their chronic infection of *Pseudomonas aeruginosa* (*P. aeruginosa*) during the winter months (Johansen 1992) The author concluded from this observation that viral respiratory tract infection may "pave the way" for colonisation and chronic infection with *P. aeruginosa*.

Description of the intervention

Many units looking after people with CF recommend that these people with CF should receive influenza vaccination. Currently available influenza vaccines give only 70% to 80% protection and have to be repeated each year. This is because the principal surface antigen haemagglutinin of the influenza virus A and B undergoes changes either by point mutation (antigenic drift) or by exchange of whole DNA segments encoding for this protein (antigenic shift). These viruses are thus capable of escaping recognition by the immune system, which acts by the production of antibodies and primed cytotoxic cells.

There are three main types of influenza vaccines currently in use: whole virus; split virus; and subunit vaccines. The first vaccine is composed of either live attenuated or inactivated whole viruses. It is considered to be the most immunogenic and many countries recommend it only for the use of adults and older children (CDC 1999). The two other types are composed of the principal influenza surface antigens, haemagglutinin and neuraminidase. These vaccine types contain less pyogenic (fever-causing) components and are therefore more suitable in paediatric use, but tend to be less effective as shown in some studies (Bernstein 1982; McElhaney 1993). Therefore, several approaches have been made to combine a subunit vaccine with a vehicle to induce a better immune response. One of these approaches is to insert the purified haemagglutinin into a membrane of liposomes. Such a vaccine is called liposomal or virosome influenza vaccine (Holm 1999).

Commonly used influenza vaccines contain two influenza A viruses or virus particles and one influenza B virus or particle (trivalent vaccine) to make them more effective. An influenza vaccine using just one virus or virus component is called a monovalent vaccine. Most studies use the measurement of antibody levels to assess the immunogenicity of the influenza vaccine. A high antibody level, however, does not imply protective immunity, as they are not the main component of the host defence against viral infection.

Why it is important to do this review

Influenza vaccines are usually well tolerated, but both local and systemic adverse reactions have been noted. There have also been a very rare report of serious adverse events, e.g. Guillain Barre Syndrome associated with influenza vaccines (HMSO 1996). There is currently no evidence on the effectiveness of vaccines for preventing influenza in people with CF.

This is an update of a previously published version of this review (Dharmaraj 2009).

OBJECTIVES

To assess the effectiveness of influenza vaccination in the management of people with CF.

We are particularly interested whether influenza vaccination:

1. improves morbidity in the 12 months after vaccination;
2. changes the rate of progression of lung function, nutritional status, numbers of intravenous antibiotic uses, *P. aeruginosa* carriage or infection and death;
3. causes adverse effects;
4. has variable effectiveness when comparing different types of vaccines.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised and quasi-randomised studies.

Types of participants

Children and adults with confirmed diagnosis of CF by sweat test or molecular genetic testing, or both, with all degree of disease severity.

Types of interventions

Vaccination with any influenza vaccine including live, inactivated, whole, split virus, monovalent, bivalent, trivalent, polyvalent A and B compared to placebo, to no intervention or to different types of influenza vaccines.

Types of outcome measures

Primary outcomes

1. Lung function measurement expressed as forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) as per cent of predicted for age, sex and height
2. Shwachman score (outcome data under point one to five following vaccination will be grouped into those measured at 0 to 3 months, 3 to 6 months, 6 to 12 months and then annually thereafter)

3. Days spent in hospital and number of hospital admission due to respiratory exacerbation

Secondary outcomes

1. Death and age of death
2. Days of antibiotic usage due to respiratory exacerbation (days of antibiotic usage per patient year)
3. Nutritional status (e.g. weight gain, body mass index, z score or others)
4. Serological response to vaccination
5. Number of participants acquiring *P. aeruginosa* infection or colonisation and time of first isolation
6. Possible adverse effects associated with the vaccination (local and systemic side effects, e.g. anaphylaxis or Guillain Barre syndrome)

Search methods for identification of studies

Electronic searches

Relevant studies were identified from the Group's Cystic Fibrosis Trials Register using the terms: vaccine AND influenza.

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*), quarterly 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 Cystic Fibrosis and Genetic Disorders Group Module.

Date of the most recent search of the Cochrane Cystic Fibrosis and Genetic Disorders Group's Cystic Fibrosis Trials Register: 08 July 2013.

Searching other resources

Additional randomised controlled studies have been found from reference lists.

The companies which market the influenza vaccines used in the trials were also contacted to obtain further information about randomised controlled trials.

Data collection and analysis

Selection of studies

Two of the authors (AT, PB) independently selected the studies to be included in the review.

Data extraction and management

Each author independently extracted data using data acquisition forms. If they had disagreed on the suitability of a study for inclusion in the review or on its quality, they would have asked the third author (RS) to assess.

If possible the authors have performed calculations on vaccination effectiveness for each vaccine type individually.

Assessment of risk of bias in included studies

Methodological quality was assessed based on a method described by Jadad (Jadad 1996), which we then related to the potential risk of bias in each study. Each author assessed the methodological quality of each study. In particular, authors examined details of the randomisation method, whether the study was blinded, whether intention-to-treat analysis was possible from the available data and whether the number of participants lost to follow up or subsequently excluded from the study was recorded. Inclusion or exclusion criteria, adverse effect reporting, statistical methods and description of dropouts were categorised as adequate or inadequate.

Measures of treatment effect

For binary outcome measures, the authors sought data on the number of participants with each outcome event, by allocated treatment group, irrespective of compliance and whether or not the participant was later thought to be ineligible or otherwise excluded from treatment or follow up to allow an intention-to-treat analysis. We aimed to calculate a pooled estimate of the treatment effect for each outcome across studies, (the odds of an outcome among treatment allocated participants to the corresponding odds among controls). For continuous outcomes, we planned to record either mean change from baseline for each group or mean post-treatment or intervention values and standard deviation or standard error for each group. For continuous outcomes we calculated a pooled estimate of treatment effect by calculating the weighted mean difference.

Unit of analysis issues

Pre- and post-vaccination antibody levels to the influenza antigen H1N1 and H3N2 at each vaccination were reported as geometric mean titre (GMT) of log2 reciprocal titres. In order to simplify the comparison the authors calculated the difference between the post-GMT and the pre-GMT (the antibody rise) with each vaccination, i.e. with the primary and subsequent vaccination.

Dealing with missing data

Further information was required on one specific study (Schaad 2000). We contacted the main author and invited him to provide the necessary information and data (Schaad 2000).

Assessment of heterogeneity

The authors tested for heterogeneity between study results using a standard chi-squared test.

The authors also considered the I^2 statistic (Higgins 2003), where the values of I^2 relate to degrees of heterogeneity as follows:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

The importance of the I^2 value depends on both the magnitude and direction of effects and also strength of evidence for heterogeneity (e.g. P value from the chi-squared test, or a confidence interval for I^2).

Assessment of reporting biases

The authors examined the study reports for adequate reporting of the study's inclusion and exclusion criteria, statistical methods and adverse effects; they also examined whether all the outcomes which were measured according to the 'Methods' section of the published papers were reported in the 'Results' section.

Data synthesis

The authors used a fixed-effect analysis to present the data. If in future updates of this review, significant heterogeneity is identified, the authors will consider analysing data using a random-effects model.

Subgroup analysis and investigation of heterogeneity

If, in future updates of this review, significant heterogeneity is identified, the authors plan to undertake subgroup analyses comparing the type of vaccine used and the degree of disease severity in participants.

Sensitivity analysis

We planned to perform a sensitivity analysis based on the methodological quality of the studies, including and excluding quasi-randomised studies.

RESULTS

Description of studies

Results of the search

The detailed search revealed six studies (Adlard 1987; Doudounakis 2000; Gruber 1994; King 1987; Ong 1991; Schaad 2000).

Included studies

Four studies met our inclusion criteria (Adlard 1987; Gruber 1994; King 1987; Schaad 2000). None of these studies compared a vaccine to a placebo or a whole virus vaccine to a split virus or subunit vaccine. Two studies compared an intranasal applied live influenza A vaccine to an intramuscular applied inactivated trivalent influenza vaccine (Gruber 1994; King 1987). These studies used also a placebo intranasal fluid and an intramuscular influenza B vaccine to enable blinding. The other two studies compare a split virus influenza vaccine to a subunit influenza vaccine (Adlard 1987) and a trivalent virosome influenza vaccine to a subunit influenza vaccine (Schaad 2000). Gruber also enrolled healthy family members into the study, but results were summarized separately from those of CF participants and were not included in this review (Gruber 1994) .

One study revaccinated those participants who had not reached sufficient antibody titres within eight weeks of their initial vaccination with a parenteral trivalent vaccine (King 1987). According to the author this was done to ensure protective cover during the influenza season. We presume that the revaccination status was not included in the analysis of post-vaccination antibody measurements.

Another study allocated the children within the virosome vaccine group randomly into four subgroups according to their age, i.e. less than six years or greater than six years and also in those receiving one or two doses four weeks apart (Schaad 2000). Participants in the subunit vaccine group were either receiving either two doses when they were aged less than six years or only one dose when they were over six years old.

Excluded studies

Two studies had to be excluded; one study was a non-randomised and non-blinded study comparing people with CF with healthy volunteers (Ong 1991) and the second study compared two different dose regimens (single dose versus two half doses) of the same influenza vaccination (Doudounakis 2000). Randomisation and blinding were also not stated.

Risk of bias in included studies

The four studies were of equal overall quality scoring (Adlard 1987; Gruber 1994; King 1987; Schaad 2000). Each scored between four to five and the possible maximum score was eight.

Allocation

It was simply stated in three studies that participants were randomly assigned, but no details given regarding the method of randomisation; the risk of bias from randomisation in these three studies is therefore unclear (Gruber 1994; King 1987; Schaad 2000). One study stated that a random number table was used; this study has a low risk of bias from the randomisation process (Adlard 1987).

None of the studies discuss allocation concealment specifically (Adlard 1987; Gruber 1994; King 1987; Schaad 2000); although Adlard states that the vaccine was 'supplied in individual syringes with pre-attached needles' (Adlard 1987). We therefore judged there to be an unclear risk of bias from allocation concealment in all studies (Adlard 1987; Gruber 1994; King 1987; Schaad 2000).

Blinding

Double blinding was achieved by two studies using placebo (Gruber 1994; King 1987) and a third study where neither participants (or their parents) nor the laboratory (outcome assessor) was aware of which vaccine had been received (Adlard 1987). These three studies therefore had a low risk of bias from blinding (Adlard 1987; Gruber 1994; King 1987). In the fourth study blinding was not possible as dose regimens in the treatment groups differed - some participants received a single injection and others received two injections. The trial was open and had a potential risk of bias (Schaad 2000).

Incomplete outcome data

In one study 64 participants were randomised, but no post-vaccination blood samples were taken from five participants and these were excluded from the immunogenicity analysis; no details were provided as to which group the excluded participants belonged (Schaad 2000). Two studies described dropouts (Adlard 1987; Gruber 1994); although Gruber only states the total numbers and does not give details of how many dropouts were in each group (Gruber 1994). Adlard describes the numbers of dropouts, states which group they had been allocated to and gives reasons (Adlard 1987). It is of note that both studies had a high total dropout rate; one with 17 out of 41 participants (41%) over the study period of three years (Gruber 1994); and the other study with 7 out of 19 (37%) of their CF participants (Adlard 1987). Both studies have included all available data into their analysis. Intention-to-treat is therefore assumed in both studies (Adlard 1987; Gruber 1994). A further study did not report dropouts, but it is evident from the total number of serum antibody levels being analysed that there were at least two

sets of data missing in each group (King 1987). It is difficult to say if this would have a significant impact on the study result (King 1987).

We therefore judge one study to have a risk of bias from incomplete outcome data (King 1987); two studies to have an unclear risk of bias (Gruber 1994; Schaad 2000); and one study to have a low risk of bas (Adlard 1987).

Selective reporting

Inclusion methods, statistical methods and adverse effects were reported adequately in all four studies, but none of these have described their exclusion criteria (Adlard 1987; Gruber 1994; King 1987; Schaad 2000). All four studies reported results for the outcome measures stated in their respective 'Methods' sections (Adlard 1987; Gruber 1994; King 1987; Schaad 2000).

Effects of interventions

Four studies enrolling a total of 179 participants with CF (143 (80%) were children aged 1 to 16 years) and 145 cases (81%) were analysed and are included in this review (Adlard 1987; Gruber 1994; King 1987; Schaad 2000).

Primary outcomes

1. Lung Function

This was not reported as an outcome measure in any of the studies.

2. Shwachman score

This was not reported as an outcome measure in any of the studies.

3. Number of hospital admissions due to respiratory exacerbation

Only one study reported this outcome measure (Gruber 1994). In the analysed study population of 15 CF participants the rate of hospital admission per 100 patient years was six in the group immunised with an intranasal live attenuated influenza vaccine versus two in the group immunised with an intramuscular inactivated influenza vaccine. Due to the high dropout rate (17 out of 41 (41%)) of CF participants it is impossible to calculate the mean number of hospital admissions per patient per year. It is therefore difficult to say if there is a significant difference between the two groups. Another study reported only four hospital admissions in their total population of 55 during the study period, but has not specified in which group these were (King 1987).

Secondary outcomes

1. Death and age of death

Only one study reported deaths (Gruber 1994). There were two CF participant deaths (one in each vaccine group) from a total of 15 analysed CF participants. The age of death was not reported.

2. Days of antibiotic usage due to respiratory exacerbation

This was not reported as an outcome measure in any of the studies.

3. Nutritional status

This was not reported as an outcome measure in any of the studies.

4. Serological response to vaccination

Pre- and post-vaccination antibody levels to the influenza antigen H1N1 and H3N2 at each vaccination were reported as geometric mean titre (GMT) of log2 reciprocal titres. In order to simplify the comparison we have entered the data where possible as the difference between the post-GMT and the pre-GMT (the antibody rise) with each vaccination, i.e. with the primary and subsequent vaccination. One study reported this outcome as a fold increase of GMT titre, but there were no analysable data provided in the study (Schaad 2000). The investigators on this study do, however, report that there were no significant differences between vaccinations (Schaad 2000). Two studies compared a live to an inactivated vaccine (Gruber 1994; King 1987); however their data could not be analysed together since both studies only presented means without standard deviations precluding analysis using RevMan 5 (RevMan 2008). The data on serological responses to vaccination from these studies can be found in the additional tables: the King data can be found in Table 1 and the data from the Gruber study are presented in Table 2. Data from the fourth study have also been entered separately in a third additional table as again only means and not standard deviations could be calculated (Adlard 1987) (Table 3). The authors of the Adlard study reported that there were no significant differences between vaccinations (Adlard 1987).

All influenza vaccinations were able to generate a satisfactory antibody rise and there were no significant differences between the vaccinations compared in the four studies.

5. Number of participants acquiring P. aeruginosa infection or colonisation

This was not reported as an outcome measure in any of the studies.

6. Adverse effects

All vaccinations used within the studies had self-reported adverse effects, either a local inflammatory reaction or a systemic effect, e.g. fever, cough or rhinorrhoea. The incidence for all reported adverse events were high depending on the symptom and vaccination type. The total adverse event rate ranged from 48 out of 201 (24%) for an intranasal live vaccine (Gruber 1994; King 1987), to 13 out of 30 (43%) for a split virus vaccine (Adlard 1987), compared to 57 out of 210 (27%) for an trivalent inactivated vaccine (Schaad 2000). None of the adverse effects were life threatening or persistent. Allowing for the low power to detect differences because of the sample size there was no significant difference between live versus inactivated vaccine, split virus versus subunit vaccine and virosome versus subunit vaccine.

DISCUSSION

This is the first systematic review on effectiveness of influenza vaccination in people with CF. We have identified four randomised controlled trials fulfilling our entry criteria. Unfortunately, there is no study currently available comparing a vaccine to a placebo or a whole virus vaccine to a split or subunit vaccine. Two of the included studies compared an intranasal applied live influenza A vaccine to a parenteral inactivated trivalent influenza vaccine (Gruber 1994; King 1987). The two remaining studies compare a subunit to a split virus vaccine (Adlard 1987) and a virosome to a subunit vaccine (Schaad 2000).

The methodological quality of the included studies was equally good. However, the data quality is impaired firstly by the low power to detect differences in adverse event rate and secondly by the high dropout rate reported in two studies. One study reported a total number of dropouts as 17 out of 41 (41%) over three years (Gruber 1994) and a second study reported 7 out of 19 (37%) dropouts over two months (Adlard 1987). The third study did not report dropouts (King 1987) and only one study had a complete follow up (Schaad 2000).

The main outcome measures reported by all four studies were adverse events (local and systemic) and immunogenicity of the influenza vaccine (measured by serological antibody response). The included studies have shown that all types of influenza vaccines used are able to generate a satisfactory immune response in people with CF. Although serological measures are not an ideal marker of protection against influenza, we did not look at influenza disease and influenza-related hospitalisation or death, as these are such rare occurrences that studies generally cannot be powered for them as outcome measures. Only one study reported hospital admission rate and death (Gruber 1994). Unfortunately none of the included studies have reported other important clinical outcome measures, such as pseudomonal infection or carriage, lung function, length of hospital stay or nutritional status. Therefore, the question if annual influenza vaccinations are clinically beneficial for people with CF remains unanswered.

The self-reported adverse events after vaccination had a wide frequency range, but none of them were serious. With the restriction of the statistical low power there is no significant difference in the adverse event rate with the vaccines used. It is difficult to generalise these findings because of the variety of components available. Two studies compared the same type of vaccinations (cold-adapted live vaccine versus trivalent inactivated vaccine) (Gruber 1994; King 1987), but used vaccines with different influenza A antigens. In fact one study used a trivalent vaccine with a different component for one of the repeated vaccination doses during this study (Gruber 1994). Comparison of the study results is therefore impossible.

AUTHORS' CONCLUSIONS

Implications for practice

According to some national recommendations and the practice in many units caring for people with CF, it is advisable to vaccinate people with CF against influenza annually. Evidence from randomised controlled studies to support this recommendation in people with CF is lacking and clinicians must make judgements on the benefits and risks of this therapy in people with CF. The cost of annual influenza vaccination may also be considered before implementing changes to current practice. In the UK in 2008 annual influenza vaccination cost £3.55 (excluding VAT) per patient per year (RLCH Pharmacy 2009).

Implications for research

There is a need for a well-designed multicentre randomised placebo controlled study of influenza vaccination in people with CF which evaluates clinically relevant outcomes. We believe that there is uncertainty about this therapy and such studies are justified. Only when improvements in clinically relevant outcomes have been demonstrated in such studies, can the results of trials comparing efficacy and safety of two types of influenza vaccines be interpreted.

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CHARACTERISTICS OF STUDIES

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

Adlard 1987

Study characteristics	
Methods	A randomised single-blind cohort study over two months.
Participants	Children (n = 19) aged 5 - 13 years with CF attending the CF clinic of the Royal Manchester Children's Hospital, UK.
Interventions	A split virion influenza vaccine (MFV Ject. Institut Merieux) versus A subunit vaccine (Fluvirin, Evans). Both vaccines were 2 IM injections given 1 month apart and contained: A/Philippines/2/82 (H3N2), A/Chile/1/83 (H1N1), B/USSR/100/83.
Outcomes	1. Adverse effects 2. Antibody levels
Notes	Antibody levels taken before and one month after vaccination.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random number table used.

Ryan 1997

Ryan F, Shortt C, Bredin C, Watson JB, O'Halloran T. The use of influenza vaccine in patients with cystic fibrosis. *Irish Medical Journal* 1997;**90**(8):293.

Smyth 1995

Smyth AR, Smyth RL, Tong CY, Hart CA, Heaf DP. Effect of respiratory virus infections including rhinovirus on clinical status in cystic fibrosis. *Archives of Disease in Childhood* 1995;**73**(2):117-20.

Wang 1984

Wang EE, Prober CG, Manson B, Corey M, Levison H. Association of respiratory viral infections with pulmonary deterioration in patients with cystic fibrosis. *New England Journal of Medicine* 1984;**311**(26):1653-8.

References to other published versions of this review

Dharmaraj 2009

Dharmaraj P, Smyth RL. Vaccines for preventing influenza in people with cystic fibrosis. *Cochrane Database of Systematic Reviews* 2009, Issue 4. Art. No: CD001753. [DOI: 10.1002/14651858.CD001753.pub2]

* Indicates the major publication for the study

Adlard 1987 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Vaccines supplied in individual syringes with pre-attached needles, but not clear if allocation concealed.
Blinding (performance bias and detection bias) All outcomes	Low risk	Parents, participants and virology laboratory not aware of which vaccine given.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Number of withdrawals from each group stated and reasons given. 7 out of 19 dropped out (37%).

Gruber 1994

Study characteristics	
Methods	A randomised double-blind placebo controlled study over 3 years.
Participants	People with CF (n = 41) and family members (n = 89) attending the Vanderbilt CF clinic, Nashville, USA.
Interventions	An intranasal live attenuated cold adapted influenza A vaccine (A/Kawasaki/9/86 (H1N1), A/Los Angeles/2/87 (H3N2) plus IM standard monovalent influenza B vaccine versus egg allantoic fluid nose drops plus IM standard trivalent inactivated influenza A vaccine (A/Taiwan/1/86 (H1N1), A/Shanghai/11/87 (or A/Shanghai/16/89 or A/Beijing/353/89 respectively) (H3N2).
Outcomes	1. Number of hospital admissions (as rate per 100 patient years) 2. Adverse effects 3. Antibody levels
Notes	Antibody levels taken before and 6 weeks after the vaccination and the following spring for each year.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as 'randomly assigned' but no details of method given.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding (performance bias and detection bias) All outcomes	Low risk	Described as double-blind. Since both treatments were given as a combination of nose drops and intramuscular injection, likely that participants and clinicians were the blinded parties.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	States number of withdrawals in total and reasons for withdrawal, but no details of which treatment group they were from.

King 1987

Study characteristics	
Methods	A randomised double-blind placebo controlled study over 1 year.

King 1987 *(Continued)*

Participants	People with CF (n = 55) attending the CF Clinic of the St Vincent's Hospital in New York, USA.
Interventions	An intranasal bivalent cold adapted influenza A vaccine (A/Dunedin/83 CR-64 (H1N1), A/Korea/1/82 CR-59 (H3N2)) plus monovalent inactivated influenza B 1 week later versus intranasal placebo plus parenteral trivalent inactivated influenza vaccine (A/Chile/83 (H1N1), A/Philippines/82 (H3N2) & B/USSR/100/83).
Outcomes	1. Adverse effects 2. Antibody level
Notes	Antibody levels taken before, 3 weeks and 7 months after vaccination.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as 'randomly assigned' but no details given as to the method.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding (performance bias and detection bias) All outcomes	Low risk	Described as double-blind, similar treatments i.e. intranasal followed by parenteral dose of active vaccine or placebo.
Incomplete outcome data (attrition bias) All outcomes	High risk	Does not report drop outs, but clear from paper that at least 2 data sets are missing from each group.

Schaad 2000

Study characteristics

Methods	An open randomised multicentre study over 4 weeks.
Participants	Children with CF (n = 64) in 5 paediatric centres in Switzerland.
Interventions	A trivalent virosomal influenza vaccine (ASingapore/6/86 (H1N1); A/Shandong/9/93 (H3N2) B/Panama/45/90) (given as either single or 2 doses 4 weeks apart) versus a trivalent subunit influenza vaccine (A/Singapore/6/86 (H1N1); A/Shandomg/9/93 (H3N2); B/Panama/45/90) (given as 1 or 2 doses 4 weeks apart).
Outcomes	1. Adverse effects 2. Antibody level rise
Notes	Antibody levels taken before and 4 weeks after the single or the second immunisation.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised, but no details of method given.

Schaad 2000 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding (performance bias and detection bias) All outcomes	High risk	Not possible as dose regimens in the treatment groups differ - some participants received a single injection and others received two injections.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	States number of withdrawals, but does not give details of which treatment group they were from or the reason for withdrawal.

CF: cystic fibrosis
IM: intramuscular

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

Study	Reason for exclusion
Doudounakis 2000	1. The study compared two dose regimens (single dose versus 2 half doses) of the same split virus vaccine. 2. Randomisation and blinding was not stated.
Ong 1991	1. The study was non-randomised and non-blinded. 2. The 2 groups enrolled to this study were not comparable: people with CF versus healthy volunteers.

CF: cystic fibrosis

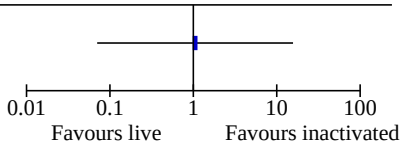
DATA AND ANALYSES

Comparison 1. Intranasal live vaccine versus intramuscular trivalent inactivated vaccine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Death	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.2 Adverse events	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.2.1 Redness	1	41	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.50, 3.02]
1.2.2 Swelling	1	41	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.28, 1.98]
1.2.3 Fever	2	96	Risk Ratio (M-H, Fixed, 95% CI)	0.42 [0.14, 1.23]
1.2.4 Rhinorrhoe	2	96	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.85, 1.63]
1.2.5 Cough	2	96	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.45, 1.67]
1.2.6 Increased Sputum Production	1	41	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.28, 1.98]

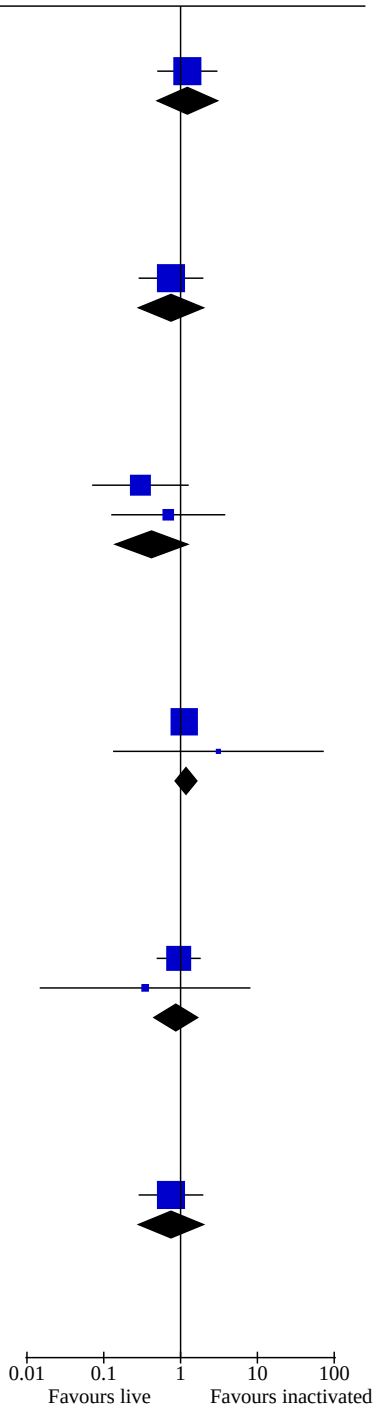
Analysis 1.1. Comparison 1: Intranasal live vaccine versus intramuscular trivalent inactivated vaccine, Outcome 1: Death

Study or Subgroup	Intranasal live Events	Total	IM inactivated Events	Total	Risk Ratio M-H, Fixed, 95% CI
Gruber 1994	1	20	1	21	1.05 [0.07 , 15.68]



Analysis 1.2. Comparison 1: Intranasal live vaccine versus intramuscular trivalent inactivated vaccine, Outcome 2: Adverse events

Study or Subgroup	Intranasal live Events	Intranasal live Total	IM inactivated Events	IM inactivated Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.1 Redness						
Gruber 1994	7	20	6	21	100.0%	1.23 [0.50 , 3.02]
Subtotal (95% CI)		**20**		**21**	**100.0%**	**1.23 [0.50 , 3.02]**
Total events:	7		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.44 (P = 0.66)						
1.2.2 Swelling						
Gruber 1994	5	20	7	21	100.0%	0.75 [0.28 , 1.98]
Subtotal (95% CI)		**20**		**21**	**100.0%**	**0.75 [0.28 , 1.98]**
Total events:	5		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.58 (P = 0.56)						
1.2.3 Fever						
Gruber 1994	2	20	7	21	69.9%	0.30 [0.07 , 1.28]
King 1987	2	27	3	28	30.1%	0.69 [0.13 , 3.82]
Subtotal (95% CI)		**47**		**49**	**100.0%**	**0.42 [0.14 , 1.23]**
Total events:	4		10			
Heterogeneity: $Chi^2 = 0.53$, df = 1 (P = 0.46); $I^2 = 0\%$						
Test for overall effect: Z = 1.58 (P = 0.11)						
1.2.4 Rhinorrhoe						
Gruber 1994	17	20	16	21	96.9%	1.12 [0.83 , 1.51]
King 1987	1	27	0	28	3.1%	3.11 [0.13 , 73.11]
Subtotal (95% CI)		**47**		**49**	**100.0%**	**1.18 [0.85 , 1.63]**
Total events:	18		16			
Heterogeneity: $Chi^2 = 0.48$, df = 1 (P = 0.49); $I^2 = 0\%$						
Test for overall effect: Z = 0.98 (P = 0.33)						
1.2.5 Cough						
Gruber 1994	9	20	10	21	86.9%	0.94 [0.49 , 1.83]
King 1987	0	27	1	28	13.1%	0.35 [0.01 , 8.12]
Subtotal (95% CI)		**47**		**49**	**100.0%**	**0.87 [0.45 , 1.67]**
Total events:	9		11			
Heterogeneity: $Chi^2 = 0.39$, df = 1 (P = 0.53); $I^2 = 0\%$						
Test for overall effect: Z = 0.43 (P = 0.67)						
1.2.6 Increased Sputum Production						
Gruber 1994	5	20	7	21	100.0%	0.75 [0.28 , 1.98]
Subtotal (95% CI)		**20**		**21**	**100.0%**	**0.75 [0.28 , 1.98]**
Total events:	5		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.58 (P = 0.56)						

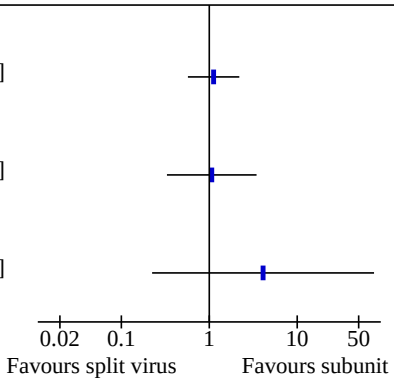


Comparison 2. Intramuscular subunit vaccine versus intramuscular split virus vaccine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1.1 Pain	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1.2 Swelling	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1.3 Fever	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 2.1. Comparison 2: Intramuscular subunit vaccine versus intramuscular split virus vaccine, Outcome 1: Adverse events

Study or Subgroup	Split virus Events	Split virus Total	Subunit Events	Subunit Total	Risk Ratio M-H, Fixed, 95% CI
2.1.1 Pain					
Adlard 1987	7	10	5	8	1.12 [0.57 , 2.20]
2.1.2 Swelling					
Adlard 1987	4	10	3	8	1.07 [0.33 , 3.45]
2.1.3 Fever					
Adlard 1987	2	10	0	8	4.09 [0.22 , 74.78]



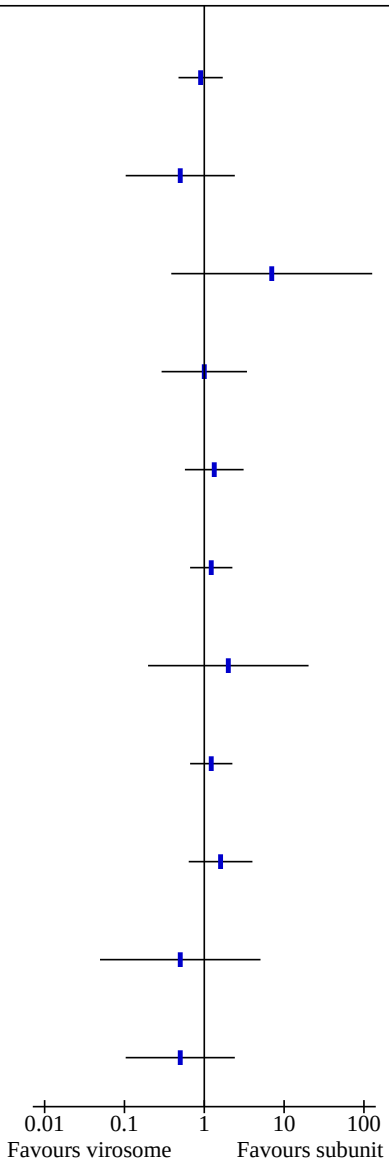
Comparison 3. Intramuscular virosome vaccine versus intramuscular subunit vaccine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Adverse events with one vaccine dose	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1.1 Pain	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1.2 Induration	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1.3 Redness	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1.4 Swelling	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1.5 Headache	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1.6 Fatigue	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1.7 Nausea	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
3.1.8 Cough	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1.9 Coryza	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1.10 Vertigo	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1.11 Irritability	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.2 Adverse events with two vaccine doses	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.2.1 Pain	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.2.2 Induration	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.2.3 Redness	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.2.4 Swelling	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.2.5 Headache	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.2.6 Fatigue	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.2.7 Nausea	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.2.8 Cough	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.2.9 Coryza	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.2.10 Vertigo	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.2.11 Irritability	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

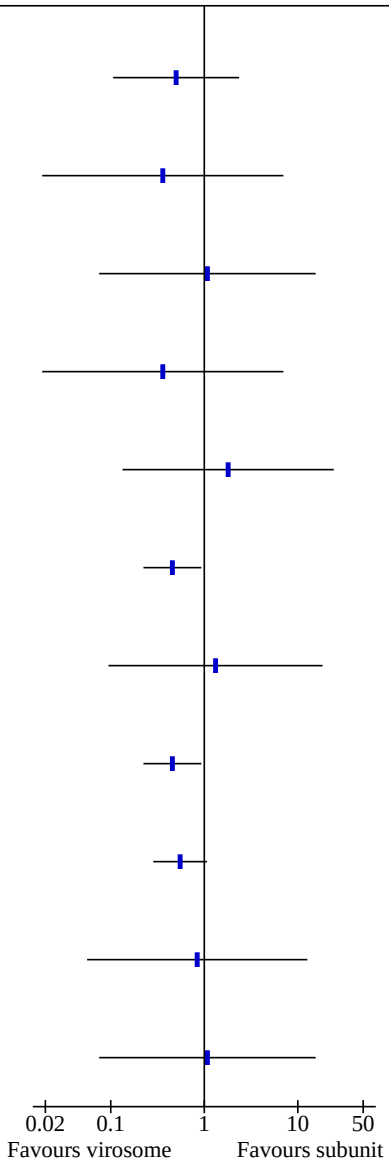
Analysis 3.1. Comparison 3: Intramuscular virosome vaccine versus intramuscular subunit vaccine, Outcome 1: Adverse events with one vaccine dose

Study or Subgroup	Virosome Events	Virosome Total	Subunit Events	Subunit Total	Risk Ratio M-H, Fixed, 95% CI
3.1.1 Pain					
Schaad 2000	9	19	10	19	0.90 [0.48 , 1.70]
3.1.2 Induration					
Schaad 2000	2	19	4	19	0.50 [0.10 , 2.41]
3.1.3 Redness					
Schaad 2000	3	19	0	19	7.00 [0.39 , 126.92]
3.1.4 Swelling					
Schaad 2000	4	19	4	19	1.00 [0.29 , 3.43]
3.1.5 Headache					
Schaad 2000	8	19	6	19	1.33 [0.57 , 3.11]
3.1.6 Fatigue					
Schaad 2000	11	19	9	19	1.22 [0.66 , 2.25]
3.1.7 Nausea					
Schaad 2000	2	19	1	19	2.00 [0.20 , 20.24]
3.1.8 Cough					
Schaad 2000	11	19	9	19	1.22 [0.66 , 2.25]
3.1.9 Coryza					
Schaad 2000	8	19	5	19	1.60 [0.64 , 4.01]
3.1.10 Vertigo					
Schaad 2000	1	19	2	19	0.50 [0.05 , 5.06]
3.1.11 Irritability					
Schaad 2000	2	19	4	19	0.50 [0.10 , 2.41]



Analysis 3.2. Comparison 3: Intramuscular virosome vaccine versus intramuscular subunit vaccine, Outcome 2: Adverse events with two vaccine doses

Study or Subgroup	Virosome Events	Virosome Total	Subunit Events	Subunit Total	Risk Ratio M-H, Fixed, 95% CI
3.2.1 Pain					
Schaad 2000	6	24	1	2	0.50 [0.11 , 2.35]
3.2.2 Induration					
Schaad 2000	1	24	0	2	0.36 [0.02 , 7.00]
3.2.3 Redness					
Schaad 2000	4	24	0	2	1.08 [0.08 , 15.52]
3.2.4 Swelling					
Schaad 2000	1	24	0	2	0.36 [0.02 , 7.00]
3.2.5 Headache					
Schaad 2000	7	24	0	2	1.80 [0.13 , 24.24]
3.2.6 Fatigue					
Schaad 2000	9	24	2	2	0.46 [0.22 , 0.93]
3.2.7 Nausea					
Schaad 2000	5	24	0	2	1.32 [0.09 , 18.42]
3.2.8 Cough					
Schaad 2000	9	24	2	2	0.46 [0.22 , 0.93]
3.2.9 Coryza					
Schaad 2000	11	24	2	2	0.55 [0.29 , 1.07]
3.2.10 Vertigo					
Schaad 2000	3	24	0	2	0.84 [0.06 , 12.63]
3.2.11 Irritability					
Schaad 2000	4	24	0	2	1.08 [0.08 , 15.52]



ADDITIONAL TABLES

Table 1. Serological response to vaccination (King 1987)

Outcome	Intranasal live		Inactivated	
	N	Mean	N	Mean
GMT rise to H1N1 with primary vaccination	21	1.1	2.5	28
GMT rise to H3N2 with primary vaccination	0.8	27	1.2	28

GMT: geometric mean titre

Table 2. Serological response to vaccination (Gruber 1994)

Outcome	Intranasal live		IM inactivated	
	N	Mean	N	Mean
GMT rise to H1N1 with primary vaccination	20	2.00	21	3.00
GMT rise to H1N1 with 1st revaccination	20	1.20	21	0.20
GMT rise to H1N1 with 2nd revaccination	20	1.30	21	1.00
GMT rise to H3N2 with primary vaccination	20	2.90	21	2.70
GMT rise to H3N2 with 1st revaccination	20	1.00	21	1.20
GMT rise to H3N2 with 2nd revaccination	20	1.40	21	2.00

GMT: geometric mean titre

Table 3. Serological response to vaccination (Adlard 1987)

Outcome	Split virion group		Subunit group	
	N	Mean	N	Mean
GMT rise to H1N1 with primary vaccination	10	228.00	9	279.00
GMT rise to H1N1 with revaccination	10	115.00	9	283.00
GMT rise to H3N2 with primary vaccination	10	520.00	9	283.00
GMT rise to H3N2 with revaccination	10	570.00	9	470.00

GMT: geometric mean titre

WHAT'S NEW

Date	Event	Description
8 April 2021	Review declared as stable	Research area no longer active.

HISTORY

Protocol first published: Issue 3, 1999
Review first published: Issue 2, 2000

Date	Event	Description
7 February 2014	New search has been performed	A search of the Group's Cystic Fibrosis & Genetic Disorders Group's Cystic Fibrosis Trials Register did not identify and potentially eligible trials.
7 February 2014	New citation required but conclusions have not changed	Minor changes regarding the latest search date have been made throughout the review.
30 March 2011	New search has been performed	A search of the Group's Cystic Fibrosis Trials Register did not identify any potentially relevant trials.
12 August 2009	New citation required but conclusions have not changed	Dr Anton Tan is no longer a member of the review team.
12 August 2009	New search has been performed	A search of the Group's Cystic Fibrosis Trials Register did not identify any trials potentially eligible for inclusion in the review.
12 August 2009	Amended	Data for serological response which had been inappropriately presented in the meta-analysis has now been presented in additional tables and narratively in the text of the Results section.
31 October 2008	Amended	Converted to new review format.
1 May 2007	New search has been performed	A search of the Group's Trials Register identified no new references for inclusion in the review. Note: A change in the lead author's surname to Dharmaraj (née Bhalla).
2 April 2006	New search has been performed	A new search of the Group's Trials Register was run, but no new references were identified. The cost of annual vaccination quoted in the section 'Implications for practice' has been updated.
2 May 2005	New search has been performed	Change of lead author from Dr Anton Tan to Dr Poonam Bhalla. Data previously entered into Statistical Analysis for the outcome 'Serological response to vaccination' for the Adlard 1987 trial have been removed. This was due to the fact that only means (without standard deviations) were reported and entered, thus generating no meaningful summary statistics. An 'Additional table' has been completed which reports these limited data that were previously entered into Statistical Analysis (Table 01).
1 January 2002	New search has been performed	The two additional studies found with literature search were the same two considered last year. Schaad 2000 has now published his study and the reference was updated accordingly. Doudounakis 2000 has presented the same study with people with cystic fibrosis from three to eight years on the European Respiratory Annual Congress 2001. This study compared two different dose regimen with the same influenza vaccine and was therefore again not eligible.
1 January 2001	New search has been performed	Two additional studies were considered for the review. However, Doudounakis 2000 was excluded as it compared two different dose regimes of the same influenza vaccination. The other study identified (Schaad 1997), which compared virosome to a sub unit vaccine, met the inclusion criteria and was incorporated into the analyses bringing the total of included studies for the review to four. Only minor changes have been made to the results with no

Date	Event	Description
		impact on the review's recommendation for further study of influenza vaccination in people with CF.

CONTRIBUTIONS OF AUTHORS

May 2005: Change of lead author from Anton Tan to Poonam Dharmaraj (née Bhalla). Anton Tan no longer remains an active author on the review.

ORIGINAL REVIEW: Anton Tan and Poonam Dharmaraj independently assessed studies for inclusion in this review.

Anton Tan acted as guarantor of the review and took the lead on the updates of the review until February 2002. Poonam Dharmaraj and Ros Smyth commented on drafts of the updated reviews.

UPDATES OF REVIEW
Poonam Dharmaraj is responsible for updating the review, with comments from Ros Smyth.

Poonam Dharmaraj acts as guarantor of the review.

DECLARATIONS OF INTEREST

None known.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

There are no differences.

INDEX TERMS

Medical Subject Headings (MeSH)

Cystic Fibrosis [*complications]; *Influenza Vaccines [administration & dosage] [adverse effects]; Influenza, Human [*prevention & control]; Randomized Controlled Trials as Topic; Vaccines, Attenuated [administration & dosage] [adverse effects]; Vaccines, Inactivated [administration & dosage] [adverse effects]

MeSH check words

Adolescent; Child; Child, Preschool; Humans; Infant