Vaccines for preventing influenza in people with asthma (Review)

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[Intervention Review]

Vaccines for preventing influenza in people with asthma

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ABSTRACT

Background

Influenza vaccination is recommended for asthmatic patients in many countries as observational studies have shown that influenza infection can be associated with asthma exacerbations, but influenza vaccination itself has the potential to adversely affect pulmonary function. A recent overview concluded that there was no clear benefit of influenza vaccination in patients with asthma but this conclusion was not based on a systematic search of the literature.

Objectives

Whilst influenza may cause asthma exacerbations, there is controversy about the use of influenza vaccinations, since they may precipitate an asthma attack in some people. The objective of this review was to assess the efficacy of influenza vaccination in children and adults with asthma.

Search methods

We searched the Cochrane Airways Group trials register and checked reference lists of articles. The last search was carried out in December 2007.

Selection criteria

Randomised trials of influenza vaccination in children (over two years of age) and adults with asthma. Studies involving people with chronic obstructive pulmonary disease were excluded.

Data collection and analysis

Inclusion criteria and assessment of trial quality were applied by two reviewers independently. Data extraction was done by two reviewers independently. Study authors were contacted for missing information.

Main results

Nine trials were initially included. Four of these trials were of high quality. Six further articles have been included in three updates (Bueving 2003; Castro 2001; Fleming 2006; Redding 2002; Reid 1998). The included studies covered a wide diversity of people, settings and types of influenza vaccination, but data from the more recent studies that used similar vaccines have been pooled.

Benefits: Bueving 2003 studied 696 children with asthma and did not demonstrate a significant reduction in influenza related asthma exacerbations (Risk Difference 0.01; 95% confidence interval -0.02 to 0.04).

Harms: The pooled results of two trials involving 2306 people with asthma did not demonstrate a significant increase in asthma exacerbations in the two weeks following influenza vaccination (Risk Difference 0.00; 95% confidence interval -0.02 to 0.02).

Authors' conclusions

Uncertainty remains about the degree of protection vaccination affords against asthma exacerbations that are related to influenza infection. Evidence from recently published trials indicates that there is no significant increase in asthma exacerbations immediately after vaccination (at least with inactivated influenza vaccination). There is concern regarding possible increased wheezing and hospital admissions in infants given live intranasal vaccination.

PLAIN LANGUAGE SUMMARY

Vaccines for preventing influenza in people with asthma

Influenza (flu) is a highly infectious disease, caused by viruses. Influenza has been thought to cause asthma attacks. Few trials have been carried out in a way that tests whether asthma attacks following influenza infection (as opposed to following the vaccination) are significantly reduced by having influenza vaccination, so uncertainty remains in terms of how much difference vaccination makes to people with asthma. The included studies suggest that the vaccine against influenza is unlikely to precipitate asthma attacks immediately after the vaccine is used.

BACKGROUND

The primary goal of influenza vaccination policy has been the reduction of excess deaths associated with influenza epidemics (Barker 1982). Mortality statistics suggest that influenza may be associated with 3,000 excess deaths per year in the United Kingdom alone and in epidemic years this may increase to as many as 18,000 (Ashley 1991). A large observational study in the United States compared expected with observed mortality during seven influenza epidemics between 1957 and 1966 with similar results (Housworth 1974). These results have consistently demonstrated the majority of excess mortality during influenza outbreaks occurs in the elderly population. The major limitations of these studies involve a lack of a direct causal link between mortality and influenza infection and the biases inherent in their retrospective research methods (Patriarca 1994).

Whilst there is still little evidence that influenza vaccination has an impact upon mortality, a randomised controlled trial of older patients (aged > 65) without known risk factors has demonstrated a 50% reduction in serologically confirmed influenza infection (Govaert 1994). A recent review advocated immunisation of all older patients (aged > 65), irrespective of risk factor status (NHS CRD 1996), despite the lack of supporting evidence for this approach. However, the current policy in the UK and many other countries is to concentrate on those who are deemed to be at higher risk including those with asthma (HMSO 1996). Recommendations for asthmatics are not supported by evidence from randomised controlled trials, and provide no indication of which sub-groups of patients with asthma, if any, should receive immunisation.

Observational studies have shown that exacerbations of asthma in children are often associated with viral infections, however there is disagreement between studies on the relative importance of influenza compared to other viruses in this respect (Johnston 1995; McIntosh 1973; Roldaan 1982). To counter the argument that immunisation might benefit patients, the potential exists for influenza vaccination to precipitate an exacerbation in some asthmatics. This is one reason why some physicians remain reluctant to recommend the vaccine for asthmatics (Rothbarth 1995).

Whilst the beneficial effect of influenza vaccine in patients with asthma may be limited and there exists some concern about potential harm, other research suggests that some asthmatics who acquire influenza infections demonstrate reductions in pulmonary functions (Kondo 1991). Therefore, immunisation has the potential to protect asthmatic patients from deterioration in lung function.

One previously published overview addressed the issue of influenza vaccination in patients with asthma and Chronic Obstructive Pulmonary Disease (Rothbarth 1995). This review concluded that there was no clear benefit of influenza vaccination in patients with asthma and COPD. A recent review (Nicholson 2003) concluded that influenza vaccination is safe in asthma. However, these results were not based on a systematic search of the published and un-

published literature. Moreover other methodological issues limit the validity of their conclusions.

The present review aims to systematically search for and combine all evidence from randomised controlled trials relating to the effects of influenza vaccination in asthmatic patients in order to generate the best available on which to base recommendations for clinical practice and further research.

OBJECTIVES

The objective of this review was to assess the efficacy and harms of influenza vaccination in children and adults with asthma.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials with or without blinding.

Types of participants

Asthmatic children (over two years of age) and adults of all degrees of severity, irrespective of living arrangements (independent, institutional, etc.). Studies reporting results on patients with COPD were excluded, but data from studies of mixed populations were included if separate data on the asthmatic patients were available from the article or following contact with the authors.

Types of interventions

Vaccination with any influenza vaccine including live, inactivated, whole, split virus, monovalent, bivalent, trivalent, polyvalent, A and B. The vaccination may have been compared with placebo, no vaccine or another type of influenza vaccine.

Types of outcome measures

Protective effects of vaccination are measured during the influenza season (late benefits), whilst adverse effects caused by vaccination are measured in the first two weeks following vaccination (early adverse effects). The following outcomes have been included under both categories:

1. Asthma exacerbations.
2. Admission to hospital (asthma related and from all causes.)
3. Pneumonia (confirmed by chest X-ray).
4. Asthma symptom scores, both in the week following immunisation and in the following six months .
5. Lung function measurements (Peak Expiratory Flow Rate {PEFR}, Forced Expiratory Volume in 1 second {FEV1}; both absolute and % predicted), both in the week following immunisation and in the following six months.
6. Number of visits to the emergency department or for other medical attention (excluding routine visits) concerning asthma in the week following injection and the following six months.
7. Number of rescue courses of corticosteroids (Prednisolone, Prednisone, Dexamethasone, and Triamcinolone) in the week following injection and the following six months.
8. Mortality (if any).

Search methods for identification of studies

Electronic searches

Trials were identified using the Cochrane Airways Group Specialised Register of trials, which is derived from systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, AMED and PsycINFO, and handsearching of respiratory journals and meeting abstracts (please see the Airways Group editorial information for further details). All records in the Specialised Register coded as 'asthma' were searched using the following terms:
((vaccin* or immuni*) and (influenza* or flu*)) or (flumist or trivalent or CAIV or LAIV or medimmune)
The most recent search was conducted in December 2007.

Searching other resources

Additionally all references in the identified trials were checked and authors contacted to identify any additional published or unpublished data. Review articles were also checked for references to missed studies.

Data collection and analysis

Titles and abstracts identified from the computerised search were assessed by two reviewers (CJC and TOJ). The full text of all potentially relevant citations was obtained for independent assessment by two reviewers (CJC and AB), who identified studies for inclusion and graded their methodological quality. Any disagreement was resolved by discussion between the reviewers. Authors were contacted for clarification where necessary.
The methodological quality of the included trials was assessed with particular emphasis on the allocation concealment, which was ranked using the Cochrane approach:
Grade A: Adequate concealment
Grade B: Uncertain

Grade C: Clearly inadequate concealment
Where there was uncertainty authors were contacted for clarification.
The agreement on methodology assessment is reported using Kappa statistics.
The methodological quality of studies was also documented using the Jadad criteria (Jadad 1996). One point is allocated for randomisation, blinding and description of withdrawals and drop-outs; an extra point can be added for methods of randomisation and blinding that are well described and adequate. Studies which use a clearly inadequate method of randomisation or blinding (such as alternating patients) lose the point allocated. The maximum score is five points and studies scoring below three points are usually regarded as being of low methodological quality. Data extraction was performed independently by two reviewers and the authors of trials contacted to provide missing data where possible. Data was checked and entered onto the computer by one reviewer.
A weighted treatment effect (using random effects) was calculated across trials using the Cochrane statistical package, RevMan version 4.2. Dichotomous outcomes are expressed as odds ratio (OR and 95% confidence intervals {CI}) and risk difference (RD with 95% CI). Continuous outcomes are expressed as weighted mean difference (WMD and 95% confidence intervals {CI}). Analyses were performed on the benefits of vaccination over the influenza season, and the short term harms experienced in the weeks following vaccination.

Cross-over trials were included along with parallel group study designs in this review. Pooling of data from these two types of trials is controversial, and this did not occur in this review. Sensitivity analyses were anticipated in the protocol, but the data were unsuitable for these purposes. Sub-group analysis of first time and repeat vaccinees were carried out, where the data allowed.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Results of the search

The original database search identified 36 abstracts for screening and 26 were selected for possible inclusion in the review. Two further papers were identified from references in other papers, (Govaert 1992; Govaert 1994). The full text of each paper was obtained and translated when necessary (three from German). Papers were excluded for the following reasons: retrospective studies (5), not randomised (5), COPD (2), no separate asthma data (5). Nine studies were included in this review with complete agreement between the two reviewers. Two further studies had been identified for the first update of this review; one was excluded as it was not randomised (Ahmed 1997) and one new study was included (Reid 1998). Four further studies were identified for the second update and have been included (Bueving 2003; Castro 2001; Redding 2002; Sener 1999). One of these studies is the subject of three papers on different aspects of the trial (Castro 2001) and the other papers are shown as secondary references.
Further searches up to December 2007 have identified 22 new abstracts; from these one large new study has been included (Fleming 2006) and authors of two other large studies on young children(Ashkenazi 2006, Belshe 2007) have been contacted to try to obtain data on the subset of children with asthma. All of the new included studies compare intranasal live attenuated vaccine to trivalent inactivated vaccine. Seven abstracts were publications relating to studies in this review, four were not randomised studies and one allocated patients to treatment by alternation (Chiu 2003). One small study was also excluded as it has not been possible to contact the authors to clarify if randomisation occurred (Kim 2003).

Included studies

See Characteristics of included studies for details.
The studies come from Europe (Bueving 2003; Fleming 2006; Govaert 1992; Hahn 1980; Nicholson 1998; Ortwein 1987; Sener 1999; Stenius 1986), Japan (Miyazaki 1993; Tanaka 1993) and the USA (Atmar 1989; Bell 1978; Castro 2001; Redding 2002). The patients studied included children (Bell 1978; Bueving 2003; Castro 2001; Fleming 2006; Miyazaki 1993; Redding 2002; Tanaka 1993) and adults (Atmar 1989; Castro 2001; Govaert 1992; Nicholson 1998; Sener 1999; Stenius 1986). Intramuscular injections of killed virus were most commonly studied, but four authors (Atmar 1989; Miyazaki 1993; Redding 2002;Tanaka 1993) studied intranasal live vaccine. Three studies included randomised comparison of different vaccine types (Fleming 2006; Nicholson 1998; Ortwein 1987).
Four studies (Bell 1978; Castro 2001; Nicholson 1998; Sener 1999) used cross-over designs, all the others were parallel groups. All studies included some outcome measures for asthma exacerbation in the early post-vaccination period, but only Govaert 1992, Miyazaki 1993, Stenius 1986 ,Tanaka 1993, Fleming 2006 and Bueving 2003 looked for late outcomes to assess the protective efficacy of the vaccine.

Risk of bias in included studies

Nine studies were of high methodological quality with a Jadad quality score of over 2 out of 5 (Atmar 1989; Bueving 2003 ;Castro 2001;Fleming 2006; Govaert 1992; Nicholson 1998;Redding 2002; Sener 1999; Stenius 1986). No placebo was used in four studies (Bell 1978; Fleming 2006; Miyazaki 1993; Ortwein 1987),

and the late outcome data from Bell 1978 was not included as it was retrospective and not randomised.

Effects of interventions

1. SPLIT VIRUS OR SURFACE ANTIGEN VACCINE v PLACEBO

BENEFITS OF VACCINATION

A study on 696 children was identified for the 2003 update of this review (Bueving 2003). This was carried out the Netherlands over two influenza seasons and in the 37 children who suffered asthma exacerbations related to positive throat swab identification of influenza virus, 20 were in the vaccinated group and 17 in the placebo group. This represents a Risk Difference of 0.01 (95% CI: -0.02 to 0.04) with a narrow confidence interval excluding a 6% absolute difference in exacerbations in the longer term following vaccination. It should be noted that a small proportion of exacerbations were related to proven influenza infection and when all exacerbations are considered the proportion of children in each group suffering an exacerbation was 85.5% in the vaccinated group and 90.1% in the placebo group; this represents a Risk Difference -0.04 (95% CI: -0.09 to 0.00), but the adjusted odds ratio in this paper did not find a significant difference between the groups (P = 0.10). The duration and severity of exacerbations were not significantly different between the two groups.

Bueving 2003 now includes subsequent publication in the European Respiratory journal of spirometry and symptom scores. These do not show a significant difference in FEV1 (% predicted) during influenza positive weeks in 41 children; mean difference 9% (95% CI: -3.86% to 21.86%). In 40 children who tested positive for influenza and had asthma quality of life measurements, there was a statistically significant difference in the change in total scores in influenza positive weeks; mean difference 0.6 (95% CI: 0.08 to 1.12). The total scores did not reach significance in "all illness" weeks. The number of patients with a change in quality of life score of at least 0.5 units (the minimally important clinical difference) was ten (48%) in the vaccine group and thirteen (68%) in the placebo group, but this change only reached significance in the symptoms and activities domains and not in the total score. Nevertheless these results do suggest a potential for influenza vaccination to be of benefit in increased asthma quality of life score associated with test-positive influenza in children.

In a previous study designed to examine late outcomes of influenza vaccination (Stenius 1986), the incidence of influenza was low in Finland during the study and only one confirmed influenza infection was detected. No differences were found between the vaccinated and control groups in daily PEFR measurements, symptom scores, daily medication, and courses of oral corticosteroids or hospitalisation in the eight months following vaccination. In one other study for which data were available from the author for asthmatic patients (Govaert 1992), none of the 25 asthmatics had serologically confirmed influenza.

HARMS OF VACCINATION

Six high quality studies contributed to the data for this outcome (Bueving 2003; Castro 2001; Nicholson 1998; Stenius 1986; Reid 1998; Sener 1999). Additional data from Bueving 2003 has been added to the outcomes for bronchodilators, medical consultation and days off school; this data comes from the report in Vaccine 2004. The pooled results failed to demonstrate any significant overall increase in asthma exacerbations in the two weeks following influenza vaccination with a risk difference of zero, (RD: 0.00; 95% CI: -0.02 to 0.02); results from two studies on 2306 patients. Similarly, the pooled results failed to demonstrate any significant difference in relation to a fall in PEFR of over 30% (RD: 0.00; 95% CI: -0.02 to 0.03), increased use of bronchodilators (RD: 0.00; 95% CI: -0.01 to 0.02) from 4 studies on 4924 patients, medical consultations (RD: 0.00; 95% CI: -0.01 to 0.02) from three studies 5092 patients, and new or increased oral corticosteroid use (RD: 0.00; 95% CI: -0.01 to 0.01).

In the earlier study on 262 patients (Nicholson 1998), with a quality score of five out of five, found a significant increase in the number of patients who suffered an exacerbation of asthma after inactivated split-virus or surface antigen vaccine administration. This was defined as a fall in PEFR of over 20%, in the first three days after injection; the risk difference was 0.031 (95% CI 0.03 to 0.058). Similarly, the number of patients with a fall of over 30% in their PEFR in the first three days after active vaccination was significantly higher than after placebo; risk difference 0.031 (95%CI 0.007 to 0.054). In a sub-group analysis, excluding patients with 'common colds' from the analysis reduced the difference to a non-significant trend, and subgroup analysis performed by the authors suggested that the majority of the exacerbations were observed in patients receiving vaccine for the first time. No other significant differences were found in the mean PEFR, bronchodilator usage (via nebuliser or metered dose inhaler), hospital admission, medical consultations, and oral steroid usage or asthma symptoms. No significant difference was reported between the results for patients given split-virus or subunit vaccines, but original data were not provided for the two groups.

The subsequent large high quality study (Castro 2001) on 2032 adults and children given inactivated influenza vaccination ruled out a significant increase in asthma exacerbations both for three days and for 14 days following vaccination. The predefined significant difference was an absolute increase of 6% (RD: 0.06) and this was outside the confidence interval for this study and for the pooled result. It was also outside the confidence interval of the pooled results for 30% fall in PEFR, increased use of bronchodila-

tors and oral steroids, and unscheduled medical consultations for asthma. Significant increase in any of these outcomes was therefore excluded for inactivated influenza vaccination in this study.
The heterogeneity between the results of Castro 2001and Nicholson 1998 is significant when the results are analysed as Peto Odds Ratios or Risk Differences. Further information has been requested from the authors of one trial (Nicholson 1998), particularly in relation to the two vaccines types used in this study. Information has been obtained from the other authors (Castro 2001) in relation to whether data are available about the previous vaccination status of the participants, indicating that first time vaccinees are not at increased risk of exacerbation in this study. Sensitivity analysis using a random effects model still excluded an important rise in exacerbations using the prespecified 6% threshold for risk difference, (RD 0.01; 95% CI -0.02 to 0.04).
In another high quality study (318 patients) which compared killed vaccine to placebo immunisation (Stenius 1986) no difference was found in the mean PEFR in morning or evening for the seven days after vaccination. No individual data on patients with a fall in PEFR of over 20% was collected.
A high quality study identified for the first update of this review (Reid 1998) compared mean FEV1 and airway responsiveness (PD20 methacholine) at 48 and 96 hours following injection of inactivated surface antigen in 17 adult asthmatic patients compared with 5 patients who were given placebo. No significant differences were found in the mean levels in either group and no patient had a change in PD20 of more than two-fold.
A small study in 24 volunteers with mild asthma (Sener 1999) found no increase in asthma symptoms or deterioration in lung function in the two weeks following vaccination with split antigen trivalent vaccine.
An early study, regarded by its authors as being preliminary (Bell 1978) also identified a significant fall (-12% from baseline, SE 6%) in morning PEFR at 48 hours after immunisation of children in a residential asthma care centre with killed influenza vaccine compared to a control group that received no vaccination. This was accompanied by a rise in nebuliser usage at 48 hours, but no change was observed in the afternoon PEFR. The original data are no longer available (Bell, personal communication), and the published results cannot be used for meta-analysis as control and treatment group data are not separately presented. Moreover, this was an open study with no placebo, randomisation by the patients' chart number and no checks for period effects were reported.
There were two other small studies in this group. No significant deterioration in home PEFR measurement was reported by Hahn using either split virus vaccine, subunit vaccine or placebo groups in the two weeks following vaccination, but no numerical data was provided (Hahn 1980). Govaert 1992 also reported no adverse symptoms from any of the 14 asthmatics immunised with split virus vaccine or the 11 asthmatics given placebo (data provided by author in response to a request for further information).

2. LIVE ATTENUATED COLD RECOMBINANT VACCINE v PLACEBO

BENEFITS OF VACCINATION

Two studies in hospitalised children from Japan documented the protective effect of vaccination during influenza outbreaks on the ward, but neither reported any outcomes associated with asthma (Miyazaki 1993; Tanaka 1993). The authors did not respond to a request for further information.

HARMS OF VACCINATION

A further high quality study on 48 children was identified for the 2003 update (Redding 2002). There was no significant difference between groups in the primary outcome of the study (percentage change in % predicted FEV-1). There was also no significant difference in the secondary outcomes of asthma exacerbations, number of participants with reduction in PEF of over 15% or over 30% and use of beta-2 agonists as rescue medication. A previously identified study (Atmar 1989) of high quality (quality score: 3 out of five) included 17 asthmatic patients. No significant differences were found in adults for hospital admission with asthma exacerbation, fall in mean FEV1, number of patients with exacerbation (fall in FEV1 of over 12% or 50 ml). This study also reported that none of the vaccine recipients reported an increase in bronchodilator therapy following vaccination, but no numerical data were provided. The pooled results from these two studies failed to demonstrate a significant difference in the risk of a drop in FEV-1 on days 2-4 post vaccination; however, the confidence interval was wide due to small numbers of participants (RD: 0.01; 95% CI: -0.12 to 0.15).
In two other studies in children (Miyazaki 1993; Tanaka 1993) both reported that no asthma attacks were apparent following vaccination, but no definition of asthma exacerbation was provided by the authors.

3. WHOLE VIRUS v SPLIT VIRUS v SUBUNIT VACCINE

In the study that compared these vaccines, the authors reported no significant difference in home PEFR measurements in the three days following vaccination in any of the vaccine groups individually or together. They also reported that there was no deterioration in lung function measured in the laboratory in the three days following vaccination (Ortwein 1987). No numerical data were provided and numbers were small (24 to 28 in each group).

4. LIVE ATTENUATED VACCINE (INTRANASAL) V TRIVALENT INACTIVATED VACCINE

A new large trial in over 2,000 children aged 6 to 17 (Fleming 2006) has been incorporated for this update. This was an open

study using intranasal vaccine (cold-adapted live attenuated influenza vaccine or CAIV-T), given by a spray applicator delivering 1 ml to each nostril. The comparison group were given trivalent inactivated vaccine (TIV) by intramuscular injection. There was no placebo group. Daily monitoring was carried out by parents or guardians for the first 15 days postvaccination; this included daily PEF and asthma symptom scores and medication. Adverse events were also recorded (for example symptoms requiring medication or an unscheduled visit to a healthcare provider), as were pre-defined reactogenicity events that could be related to vaccination (such as runny nose and wheeze).

BENEFITS OF VACCINATION

Since there was no placebo arm in this study the absolute benefit of CIAV could not be assessed. In comparison with TIV, there was no significant difference in the rate of asthma exacerbations between intranasal and intramuscular vaccines over the full duration of the study [incidence 31% v 30%, difference 1.6% (95% CI: -2.2 to 5.4%). There were two hospitalisations for respiratory illness with TIV and none with CIAV; this was not a significant difference, [Odds Ratio 0.2, (95% CI 0.01 to 4.17)]. There was a marginally significant difference between groups for days off school, [rate ratio 1.09 (95% CI 1.0 to 1.2)], but no significant differences for unscheduled health care visits or children with serious adverse events (1.8% with CIAV and 1.7% with TIV).

HARMS OF VACCINATION

In the first 15 days there was a significant increase in children reporting runny nose after the intranasal vaccine [66% v 53%, Odds Ratio 1.78 (95% CI: 1.50 to 2.11)], and the increase was also significant in those reporting rhinitis as an adverse event [9% v 5%, Odds Ratio 1.76 (95% CI: 1.27 to 2.44)]. This has to be balanced against 60% of children who reported pain from the injection site with the intramuscular injection. In terms of bronchospasm reported as an adverse event there was no significant difference between groups [3% in both groups, Odds Ratio 1.03 (95% CI: 0.62 to 1.72)]. There was, however, less wheeze reported in the first 15 days with intranasal vaccine [18% v 22%, Odds Ratio 0.79 (95% CI; 0.64 to 0.97)]. No significant difference was found between exacerbation rates in the two groups over the first 42 days following vaccination; the risk difference -0.1 percentage points, (95% CI: -2.8 to 2.6 percentage points).

It appears that in children aged 6 to 17 years of age intranasal and intramuscular vaccines have similar profiles for asthma exacerbations and wheeze of sufficient severity to be considered an adverse event. Two further studies (Ashkenazi 2006; Belshe 2007) were found comparing intranasal vaccine with intramuscular vaccine in children from 6 to 71 months of age; some of these children had a clinical diagnosis of asthma and further information has been sought from the authors on this subgroup of children. Concern was raised in the Belshe 2007 study as the new intranasal vaccine was associated with an increase in hospital admissions in children from six to 11 months [6.1% versus 2.6% over 180 days; rate difference 3.5% (95%CI 1.4 to 5.8%)], and more episodes of medically significant wheezing in the first 42 days following the vaccine (2.3% versus 1.5%; rate difference 0.77% [95% CI, 0.12 to 1.46]).

DISCUSSION

This systematic review examines the effectiveness of influenza vaccination in patients with stable asthma. Despite employing an exhaustive search, few articles were identified that met methodological inclusion criteria. Whilst this review is largely descriptive in nature, the potential for short term adverse effects and long term benefits can be summarised. There are now two large cross-over trials assessing the adverse effects of split virus or surface antigen influenza vaccination on asthma (Castro 2001; Nicholson 1998). Overall, it is reassuring that the likelihood of an asthma exacerbation following influenza vaccination is small, and that the absolute difference in risk of exacerbation between active vaccination and placebo lies between a 2% reduction and 2% increase. The excess of early exacerbations in one study (Nicholson 1998) following first time vaccination remains unexplained.

On the other hand the data from the new trial on longer term benefit of influenza vaccination in the prevention of asthma exacerbations caused by exposure to influenza virus in the community is disappointing (Bueving 2003). The authors failed to demonstrate a significant benefit in children in the Netherlands in two seasons of exposure and the absolute benefit of vaccination from this trial lies between a 3% reduction and a 4% increase in exacerbations related to proven influenza infection. Again this confidence interval excludes the pre-determined 6% difference used by Castro in their power calculation (Castro 2001). The point estimate for the difference in all exacerbations is a 4% reduction in risk, but the confidence interval includes no difference between groups and a 9% risk difference. Consequently, there is no firm evidence from controlled clinical trials to support the adoption of universal vaccination in patients with asthma as a clinical policy. More recent information has now been published on asthma symptoms during influenza positive illness weeks in Bueving 2003, indicating that the asthma quality of life scores in such weeks may be improved by influenza vaccination (in 40 of the 696 children who had confirmed influenza infection).

Several new large studies have been identified comparing intranasal vaccine to intramuscular injection in children aged 6 to 17 years (Fleming 2006), and in infants from 6 to 72 months (Ashkenazi 2006; Belshe 2007). There was no indication of an increase in adverse respiratory outcomes in the older children, but one of the

studies on infants (Belshe 2007) has raised concerns over increased wheezing and hospital admissions following intranasal vaccination in the younger age group.

METHODOLOGICAL LIMITATIONS

1. The trials identified in this review represent a wide diversity of patients, settings and types of influenza vaccine. Initially most of the trials involved small numbers of patients, but the review has now been strengthened by the addition of two new larger placebo controlled trials of high methodological quality (Castro 2001; Bueving 2003).
2. Influenza vaccination is administered at a time of year when upper respiratory viral infections are common; these can cause symptoms and asthma exacerbation which may occur soon after vaccination. The importance of good placebo control is demonstrated in the one study, (Atmar 1989), in which four of the six patients from the placebo group had an illness in the week following the vaccination. One patient from the placebo group was also admitted to hospital with an asthma exacerbation. This problem was addressed in the Nicholson study (Nicholson 1998). The authors re-analysed their data after excluding patients with symptoms of upper respiratory tract infection in order to minimise the risk of including patients with exacerbations due to viral illness.
3. Many studies did not report numerical outcomes for use of bronchodilator therapy and worsening of asthma symptoms. This data is therefore included in tables of results in the section "Other Data". Reports of "no significant difference" may hide small effects which become important when pooled, however, such comments are not useful without the data from which they are derived. Our attempts to contact the authors met with limited success, as most did not reply to a letter and a fax requesting further details.
4. The use of mean values for lung function data and asthma symptoms is of limited value as individual changes in important specific outcomes (i.e. asthma exacerbations or pulmonary function) may be missed.
5. The proportion of asthmatic patients who might contract influenza in a non-pandemic winter may be small, and similarly the proportion suffering an adverse event from the vaccine may also be low. One study (Stenius 1986) identified only one serologically confirmed case of influenza among 157 asthmatics who were given a placebo vaccination. In another, (Govaert 1994) none of the 11 asthmatics given placebo developed serologically confirmed influenza, and in the total 911 elderly patients given placebo only 9% went on to develop serologically confirmed infection. Of those patients who develop influenza not all would be expected to develop asthma exacerbations.

6. Many other respiratory viruses can cause asthma exacerbations. One observational study (Nicholson 1993) found that in 27 adults with viral infections leading to a fall of over 50 L/min in PEFR, only one was due to confirmed influenza virus (compared to 16 in which human rhinovirus was confirmed). Similarly, in children aged 9 to 11 years old, common cold viruses were identified in 80% of reported asthma exacerbations; influenza viruses were detected seven times less commonly in exacerbations (Johnston 1995). It is therefore important that any exacerbations following a flu-like illness are only regarded as being due to influenza only if this is confirmed by a rise in antibody titre or virus detection, such as carried out in Bueving 2003.

CLINICAL PRACTICE

The potential impact of influenza vaccine will depend upon the frequency with which this virus causes acute exacerbations and infections in asthmatic individuals. This may also vary between epidemic and non-epidemic years. Such data are not available. Interpretation of the protective effects of influenza vaccines has to be viewed within this background.

Protective effect of vaccination:

There are very limited data from randomised controlled trials available to assess the protective effect of influenza vaccination in asthma. Only two studies of high quality used clinically important outcomes to test for a reduction in asthma exacerbations following influenza vaccination (Stenius 1986; Bueving 2003). Significant benefit in terms of reducing asthma exacerbations caused by influenza virus infection has not been demonstrated, although there is now a suggestion of a benefit in asthma quality of life scores in relation to episodes of proven influenza infection in a small number of children.

Comparison of Vaccine types:

Randomised comparison of different vaccination types was carried out in three studies looking for short term adverse effects (Nicholson 1998; Hahn 1980; Ortwein 1987), but reporting of the outcomes was restricted to "no significant differences" found between groups.

Asthma exacerbation following vaccination:

A higher incidence of asthma exacerbations following killed influenza vaccination was found in one study (Nicholson 1998), with a Risk Difference of 3.1% (95% CI 0.3% to 5.8%) compared to placebo. This study was methodologically strong and was designed to identify patients in which common colds might explain the exacerbation. When patients with upper respiratory tract infections were excluded the difference was no longer significant. It is not possible to say whether the risk difference was less, as the total number of patients excluded from each group due to colds

was not reported. The authors conclude that the risk of exacerbation is low in comparison to the possible protective effect of the vaccine. This has not been borne out by the subsequent trial from the Netherlands (Bueving 2003). The recent large study on split virus vaccine (Castro 2001) gives reassurance in terms of the safely of this type of influenza vaccination. More recently three large studies in children (Fleming 2006; Ashkenazi 2006; Belshe 2007) have compared intranasal vaccine with intramuscular injection in infants and older children. The results in older children are reassuring, but there is concern about increased wheezing and hospital admission in infants given intranasal vaccine.
The other high quality studies (Atmar 1989; Redding 2002) which measured individual exacerbations following recombinant vaccine failed to demonstrate a significant difference between the vaccinated and placebo groups; however, the pooled results were underpowered to detect the risk difference of 3% found in the Nicholson study.

Implications for research

1. Further large randomised controlled trials are needed to determine whether there is a protective effect of influenza vaccination in ambulatory adults and children with stable asthma. The trial should have sufficient power to detect infrequent exacerbations (such as the 6% risk difference used by Castro) due to the immunisation or influenza infection, and changes in asthma quality of life in relation to proven influenza infection.

2. Future trials should include an analysis of exacerbation rate using recognised methods and definitions for detecting asthma exacerbations, and verification of influenza exposure. Other important asthma related outcomes should also be reported, such as hospital admission, rescue courses of oral corticosteroids, and unscheduled attendance in primary care or emergency departments.

AUTHORS' CONCLUSIONS

Implications for practice

1. The evidence available from randomised controlled trials has failed to identify a reduction in the frequency of asthma exacerbations following influenza infection, but one study has now demonstrated improved asthma quality of life scores in a small number of children with confirmed influenza infection.

2. Overall, influenza vaccination appears safe in adults and older children with asthma; a significant increase in asthma exacerbations immediately following split-virus influenza vaccination has now been excluded. No significant difference has been identified between vaccine types in these age-groups. However, there are insufficient trials and the number of patients upon which these comparisons are based is small.

3. Intranasal vaccination in children under two years of age may be associated with increased wheezing and hospital admission.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Atmar 1989

Methods	Randomisation: no details. Blinding: double-blind, but no details of method used. Number excluded: no details. Withdrawals: 2 (one from each group due to extraneous viral infection.) Baseline characteristics: antibody levels to influenza A and B measured and baseline lung function tests. Jadad score:3
Participants	Location:Houston, Texas. Participants: 19 healthy adult volunteers with a history of asthma. 17 had data analysed, 11 given vaccine and 6 placebo. Asthma definition and severity: history of intermittent wheezing, 15 patients using intermittent or continuous bronchodilator therapy. Exclusion criteria: acute respiratory illness, allergy to egg, pregnancy
Interventions	Vaccine Type: Intranasal bivalent (H3N2+H1N1) influenza A vaccine. 0.25 ml per nostril. Placebo: Allantoic fluid, 0.25 ml per nostril.
Outcomes	Early: Lung function tests on days 0, 3-4, and 7; performed in the mornings (no bronchodilators taken before testing). The authors regarded a reduction in FEV1 of 13% (or greater) from baseline to be clinically significant. Bronchodilator therapy and hospital admission were also reported
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Information not available (Cochrane Grade B)

Bell 1978

Methods	Randomisation: by hospital number Blinding: none (cross-over with no placebo) Number excluded: no details Withdrawals: none Baseline characteristics: not compared. Jadad score:1
Participants	Location: Denver, Colorado. Residential Asthma Care Centre. Number and age of participants: 79 children (age 6 to 16 years) in residential centre. Asthma definition and severity: reversible obstructive airways disease, moderately severe (two thirds on long-term corticosteroids).

Bell 1978 (*Continued*)

	Inclusion criteria: not received influenza vaccine prior to admission to the centre. Exclusion criteria: allergy to egg.
Interventions	Vaccination Type: Bivalent (A/Port Chalmers/1/73 and B/Hong Kong/5/72) vaccine containing killed influenza virus. 0.25 ml or 0.5 ml given. Placebo: none crossover trial with 2 week washout)
Outcomes	Early: Change in peak flow and mean number of nebulised treatments given. Late: Not included as no randomisation and retrospective data audited
Notes	First arm of crossover trial included. Data expressed as Mean difference in % change in predicted Peak Flow, and Nebuliser usage, between vaccinated and non-vaccinated groups. SD calculated from published SEM. CAUTION: No baseline comparability of the two groups is reported

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	No	Study investigators aware as to order of treatment group assignment (Cochrane Grade C)

Bueving 2003

Methods	Randomisation took place by the manufacturer when packing vaccine and placebo, from a computer generated list. Blinding: double-blind with active or placebo vaccines used Number excluded: 696 children enrolled out of 3220 invited by GPs Withdrawals: 3 lost diaries from vaccine group and 5 from placebo group Baseline characteristics: comparable Jadad score:5
Participants	Location: Rotterdam, Netherlands community based study. Number and age of participants: 696 children aged 6-18 years; mean age 10.5 years (SD 3.2) Asthma definition and severity: children selected from GP files based on prescribed asthma medication. Mean FEV1 89% predicted and 16% had ever been hospitalised for asthma Inclusion criteria: maintenance therapy for asthma (inhaled corticosteroids or cromoglycate), or more than 52 doses of relief medication during the previous 12 months Exclusion criteria were other chronic diseases, allergy to chicken protein and insufficient understanding of the Dutch language
Interventions	Vaccination type: inactivated influenza vaccine intramuscular injection. The vaccine composition for 1999-2000 was a combination of A/Sydney/5/97 H3N2-like, A/Beijing/262/95-like and B/Beijing/184/93-like strains and for 2000-2001 A/Moscow/10/99 H3N2-like, A/New Caledonia/20/99 H1N1-like and B/Beijing/184/93-like strains as advised by the World Health Organisation Placebo group: The placebo consisted of a buffered phosphate solution with the same pH value and similar appearance as the inactivated influenza vaccine

Bueving 2003 (*Continued*)

Outcomes	Primary outcome: Influenza-related asthma exacerbations (number, duration and severity). Secondary outcomes were adverse effects of the vaccination including airway symptoms, the number, duration and severity of all asthma exacerbations, proportion of days with symptoms of upper respiratory tract (URTI) and/or lower respiratory tract (LRT), use of asthma medication and other medication, consultations of a specialist or GP, admittance to hospital for airway problems, rising of antibody-titre against influenza, and the number of serologically proven influenza infections
Notes	Power calculations suggested 600 patients needed to be enrolled

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	Study investigators unaware as to order of treatment group assignment (Cochrane Grade A)

Castro 2001

Methods	Cross-over design. Randomisation: central pharmacy labelled injections and kits Blinding: double blind, contents of syringes not divulged until the end of the trial Number excluded: no details Withdrawals: reported 2009 out of 2032 received both injections Baseline characteristics: only reported for the whole study population Jadad score: 5
Participants	Location: 19 centres in the USA Participants: 1240 adults and 712 children with (mostly with mild-to-moderate persistent asthma). Asthma was physician diagnosed. Inclusion criteria: stable asthma taking prescribed asthma treatment in preceding 12 months, with no exacerbations in previous 2 weeks. Exclusion criteria: allergy to egg or thiomersal, inability to use peak flow meter, no telephone, history of Guillan-Barre syndrome, influenza vaccination in previous 6 months, febrile illness in preceding 24 hours
Interventions	Vaccination type: Heat-killed trivalent split-virus influenza type A and B vaccine (Fluzone, Aventis-Pasteur) . Placebo: identical syringe containing saline. Random order of injections with 4 weeks between doses.
Outcomes	Primary outcome: Exacerbation of asthma within 14 days of vaccination. (Definition as one or more of PEF fall of 30% or more from personal best, increase in daily use of albuterol above average use reported in 2 weeks before randomisation [4 or more puffs or 2 nebulisations for relief of symptoms], increase in systemic steroids, unscheduled use of health care for asthma) Secondary outcomes: Decrease of >20% from best personal PEF, average PEF, symptoms, days off school or work, increase in preventer medication

Castro 2001 (*Continued*)

Notes	Bubble sizes were noted to be larger in the placebo syringes. Authors provided unpublished data on exacerbations in first time and repeat vaccinees

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	Study investigators unaware as to order of treatment group assignment (Cochrane Grade A)

Fleming 2006

Methods	Design: Parallel, open-label study designed to test non-inferiority Duration: October 2002 until May 2003 Number of arms: two Run-in period: seven day screening period in which asthma parameters were assessed Placebo or active control group: active
Participants	Location: 145 study sites in Europe Number of participants randomised: live intranasal vaccine 114, injectable vaccine 115 Age of participants: 6 to 17 years Inclusion criteria: Clinical diagnosis of asthma with one or more prescriptions for asthma in the past 12 months (including antibiotics for respiratory illness associated with a wheezing episode) Exclusion criteria: serious chronic disease, disease of the immune system or current immunosuppressive drugs (including high-dose systemic corticosteroids)
Interventions	Arm 1: Live attenuated influenza vaccine (CAIV-T) Arm 2: Injectable trivalent inactivated influenza vaccine (TIV)
Outcomes	Primary outcome of the study: culture confirmed influenza caused by a subtype that was antigenically similar to the vaccine. The primary safety end point was the incidence of asthma exacerbation, defined as acute wheezing illness associated with hospitalization, any unscheduled clinical visit, or any new prescription (including rescue medication). Secondary outcomes: Influenza due to any subtype, prescribed medication, unscheduled healthcare visits, hospitalisations, days missed from work or school. Secondary safety end points were (1) recurrent episodes during the surveillance period of acute wheezing illness associated with hospitalization, unscheduled clinical visit, or increased or new asthma medication use (medically required increase in daily dosage of currently prescribed asthma medication or newly prescribed asthma medication); (2) the first asthma exacerbation episode within 42 days; (3) PEFR scores; (4) nighttime awakenings (or sleep scores); and (5) asthma symptom scores. Time of measurements: Early (first 15 days), Medium (first 42 days) and Late (from 15 days up to May the following year) Reliability of measurements: unreported Source of extracted data: Paper publication
Notes	Sequence generation adequate: Automated interactive voice response system Allocation concealment adequated: Automated interactive voice response system

Fleming 2006 (*Continued*)

	Blinding none: Open label study Incomplete outcome data was addressed adequately: Only seven patients failed to complete the study Freedom from selective reporting is unclear: Reporting of results in the paper makes it difficult to separate early and late asthma exacerbations; adverse event data for wheeze in the first 15 days has been used, but no exacerbation data is given for the first 15 days Funding was from MedImmune and Wyeth (who manufacture the intranasal vaccines)

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	Study investigators unaware as to order of treatment group assignment (Cochrane Grade A)

Govaert 1992

Methods	Randomisation: Stratified by four morbidity categories Blinding: Double-blind Exclusions: Those in high risk groups (25 asthmatics were however included in the study) Withdrawals: none but one patient in the placebo group had incomplete data. Baseline characteristics: no data Jadad score: 5
Participants	Location: Netherlands Patients were all aged 60 or over. Of the 1838 patients participating in the study 25 had asthma (no details of definition or severity but severe cases likely to have been excluded). Of these 14 received vaccine and 11 received placebo. Exclusion criteria: Age under 60, living in old peoples' homes or nursing homes, belonging to a high risk group (interpreted differently by general practitioners)
Interventions	Vaccination type: purified split vaccine H1N1, H3N2, B45/90, B1/87 given intramuscularly. Placebo:Physiological saline intramuscularly.
Outcomes	Early: adverse reactions (recalled by the patients after 4 weeks). Late: Serologically confirmed influenza.
Notes	No serologically confirmed influenza was seen in either the immunised or the placebo group

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	Study investigators unaware as to order of treatment group assignment (Cochrane Grade A)

Hahn 1980

Methods	Randomisation: Stratified by baseline FEV1 (no details of allocation concealment) Blinding: single blind Number excluded: no details Withdrawals: not stated Baseline characteristics: FEV1 comparable in each group Jadad score: 1
Participants	Location: Wurzburg, Germany Number and age of participants: 52 asthmatic patients (age not stated) Asthma definition and severity: Reversible airways obstruction. 9 included patients used systemic steroids. Inclusion criteria: 20% rise in FEV1 following Fenoterol, or 20% spontaneous change in FEV1 recordings or documented breathing difficulty with deterioration in lung function
Interventions	Vaccination types: 1. Split virus vaccine A/90/70, A/1/77, B/8/73 (injection in deltoid) 2. Subunit vaccine A/92/77, A/1/77, B/8/73 (injection in deltoid) Placebo: Saline injection (in deltoid)
Outcomes	Lung function measurements in Clinic, (two weeks before and after treatment). Home measurement of peak flow (best of three, twice daily) and symptoms recorded by patients (including breathing difficulty)
Notes	No lung function measurements documented, only "no significant change in lung function following either vaccination or placebo" (even in the patients on systemic steroids)

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Information not available (Cochrane Grade B)

Kut 1999

Methods	Randomisation: no details Blinding: placebo saline injection given Number excluded: not stated Withdrawals: not stated Baseline characteristics: similar PC20 at baseline Jadad score:3
Participants	Location: Istanbul, Turkey Number and age of participants: 59 asthmatic children, all atopic, aged 6.5 to 15 years. Asthma definition and severity: no details Inclusion criteria: symptom free in the past 2 weeks. Exclusion criteria: no details
Interventions	Vaccination type: Inactivated influenza vaccine given subcutaneously Placebo: saline subcutaneously

Kut 1999 (*Continued*)

Outcomes	PC20 for methacholine challenge before vaccine and after 24 hours. Daily peak flow, symptoms and rescue medication in the week after vaccination
Notes	PC20 (SD) in the placebo group was 7.02 (9.3) before challenge and 7.3 (3.6) after 24 hours. In the vaccine group PC20 was 9.5(10.6) before vaccine and 9.8(9.3) afterwards

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Information not available (Cochrane Grade B)

Miyazaki 1993

Methods	Randomisation: no details Blinding: none (no placebo) Number excluded: not stated Withdrawals: none Baseline characteristics: serology only Jadad score:1
Participants	Location: Minami-Fukuoka chest hospital, Japan. In-patients on asthma ward. Number and age of participants: 49 children mean age 11.1 years (SD 2.7) Asthma definition and severity: institutionalised asthmatic children Inclusion criteria: in-patients on the asthma ward Exclusion criteria: allergy to eggs or chicken feathers
Interventions	Vaccination Type: intranasal cold-adapted recombinant trivalent influenza vaccine (H1N1, H3N2, B). Dose 0.3 ml by nasal spray. Placebo: none
Outcomes	Early: asthma attacks Late: febrile illness with 4 fold rise in antibody titre.
Notes	Serology at the start was NOT comparable with 17/19 in the vaccinated group having a starting titre over 1:64 whereas only 8/25 in the non-vaccinated group had a starting titre over 1:64

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Information not available (Cochrane Grade B)

Nicholson 1998

Methods	Randomisation: sealed envelopes, computer-generated randomisation code provided by vaccine manufacturer. Blinding: double-blind Number excluded: 74 out of 361 patients who agreed to participate Withdrawals: 25 (8 withdrawn and 17 excluded due to missing data) Baseline characteristics: comparable PEF in both groups. Possible order effects and interactions were explored by ANOVA; none were found in the primary analyses. Jadad score: 5
Participants	Location: nine respiratory centres and two asthma clinics in the United Kingdom. Number and age of participants: 287 adults randomised, aged 19-75 years (median 51.7 years). Asthma definition and severity: "recurrent episodes of airway obstruction that resolved on treatment" as diagnosed by a clinical specialist. 90% were on inhaled corticosteroids and 17% on maintenance oral steroids. Mean PEF at baseline was 67% predicted. Inclusion criteria: stable asthma (requiring no active revision of medication). Exclusion criteria: hypersensitivity to eggs, chicken or influenzal protein. Treatment with an investigational drug during the 30 days before recruitment
Interventions	Crossover design with two intramuscular injections given two weeks apart in random order. Vaccination Types: Two trivalent vaccines containing either inactivated split-virus or surface antigen preparations containing 15 mcg of haemagglutinins to A/Singapore/6/86 (H1N1), A/Johannesburg/33/94(H3N2) and B/Beijing/184/93. Placebo: phosphate-buffered solution and saline (in identical syringes)
Outcomes	Outcome measures: primary clinical outcome was an asthma exacerbation within 72 hours of injection (defined as 20% fall in Peak Flow compared to lowest of the three days before vaccination). Also measured were change in mean PEF, inhaled Beta-agonist use (72 hours before and after injection), antibiotic and oral steroid use for 7 days after injection, unscheduled medical attendance and hospital admission for 7 days after each injection. Symptom scores were also analysed for 72 hours before and after injection of vaccine or placebo
Notes	Peak flow was examined using percentage change for individuals of the worst test for 3 days before and after injection and also using the mean test result over the same periods. On all occasions only the best of three blows was used for the analysis

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	Study investigators unaware as to order of treatment group assignment (Cochrane Grade A)

Ortwein 1987

Methods	Randomisation: Stratified by lung function results Blinding: uncertain Number excluded: no details Withdrawals: no details Baseline comparison: not reported Jadad score: 1
Participants	Location: Germany Number and age of participants: 80 asthmatics (?age) 28 given whole virus, 24 split virus and 28 subunit vaccine. Asthma definition and severity: "reversible airways obstruction" stratified by %FEV1 Inclusion/Exclusion criteria: no details
Interventions	Vaccination type: Whole virus, Split virus and Subunit vaccines. (A/Texas, A/USSR, B/Hong Kong). Patients were revaccinated at 6 weeks. No Placebo group in the study.
Outcomes	Pulmonary function measured for 7 days before vaccination and compared with 3 days after vaccination. Daily home peak flow measurements before and after vaccination
Notes	No placebo group and results stated as "no significant change in Lung function for individual or for the combined vaccines."

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Information not available (Cochrane Grade B)

Redding 2002

Methods	Randomisation: computer generated random numbers Blinding: double-blind (intranasal placebo used) Withdrawals: none Baseline: comparable Jadad score: 4
Participants	Location: Two paediatric allergy practices in Seattle (Washington) and one in Stockton. Participants: 48 children and adolescents (aged 9 to 17 years). 75% Caucasian in placebo group and 96% Caucasian in vaccinated group. Asthma definition and severity: Reversibility testing (>12% increase in morning FEV1 after albuterol), with FEV1 <80% predicted after withholding albuterol for 8 hours. Mean FEV1 75% predicted. Exclusion criteria: intranasal corticosteroids, allergy to egg, acute febrile illness within one week, diagnosed with other pulmonary disease
Interventions	Vaccination type: Intranasal influenza virus trivalent, types A and B, live, cold-adapted (CAIV-T). Dose: single dose of 0.25 ml to each nostril Placebo: Egg allantoic fluid with sucrose-phosphate glutamate

Redding 2002 (*Continued*)

Outcomes	The primary outcome index was the percent change in percent predicted FEV1 before and after vaccination. Peak flows, clinical asthma symptom scores and nighttime awakening scores were measured daily from 7 days pre- to 28 days postvaccination
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	Information not available (Cochrane Grade B)

Reid 1998

Methods	Randomisation: no details. Blinding: double-blind, but no details of method used. Number excluded: no details. Withdrawals: none Baseline comparison: 13 out of the 22 participants had received influenza vaccine before but no data on how these fell into the vaccine or placebo groups. Mean FEV1 was 17% higher in the placebo group. Jadad score: 3
Participants	Location: Newcastle, UK Participants: 22 adults aged 19 to 71 years. 17 were randomised to vaccine and 5 to placebo. Asthma definition and severity: all had FEV1 >60% predicted and >15% reversibility; all took inhaled beta-agonists and 20 took inhaled steroids. All were non-smokers and 13 had previously received influenza vaccination. Exclusion criteria: none mentioned.
Interventions	Parallel design double blind. Vaccine type: Inactivated surface antigen influenza vaccine 0.5 ml deep subcutaneous injection (Evans Medical Ltd). Placebo: no details of placebo vaccination
Outcomes	Spirometry (FEV1) and airways responsiveness (PD 20 methacholine). Both were measured twice at an interval of two weeks before vaccination and compared with measurements at 48 and 96 hours post-vaccination
Notes	Data presented without standard deviations. The study was powered to detect a halving of the geometric mean PD 20

Risk of bias

Item	Authors' judgement	Description

Reid 1998 (*Continued*)

Allocation concealment?	Yes	Study investigators unaware as to order of treatment group assignment (Cochrane Grade A)

Sener 1999

Methods	Randomisation: no details Blinding: single-blind (but much higher local reaction rate in vaccine group may have compromised this) . Withdrawals: none Baseline comparison: no described Jadad score: 3
Participants	Location: Ankara, Turkey Participants: 24 volunteers with mild stable asthma. Mean age 39 years. 19 women. All non-smokers. Mean FEV1 100 % predicted (range 73 to 150). Exclusion criteria: pregnancy, acute respiratory illness, allergy to eggs
Interventions	Cross-over design, single blind. One week wash-out period. Vaccine type: inactivated trivalent split antigen (Pasteur Merieux) 0.5 ml intra-muscular injection. Placebo: Saline placebo.
Outcomes	Asthma symptoms, morning and evening PEF, bronchodilator use all for one week following vaccination. Spirometry with methacholine challenge at baseline and 2 weeks after vaccination
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	Information not available (Cochrane Grade B)

Stenius 1986

Methods	Randomisation: stratified into three age groups (15-29, 30-49, 50 or more) Patients selected themselves by choosing a folded piece of paper marked A or B inside. Blinding: double-blind. Identical ampoules used with a code locked in the vaccine laboratory. Number excluded: no data Withdrawals: 328 recruited, 10 withdrew in first week, 27 in total lost to later follow-up. Baseline characteristics: comparable for asthma and influenza serology Jadad score:5
Participants	Location: 9 centres in Finland, asthmatic patients living in the community. Number and age of participants: 328 adults (age 17-73) Asthma definition and severity: moderate to severe asthma in need of daily treatment, all patients fulfilled the criteria for bronchial asthma set by the American College of Chest Physicians and the American

Stenius 1986 (*Continued*)

	Thoracic Society. Inclusion criteria: ability to make reliable PEF measurements, non-smokers for past two years, stable asthma for past two weeks, no viral infections for past six weeks. Exclusion criteria: egg allergy, immunotherapy treatment, treatment with regular beta-blockers or over 10 mg prednisolone daily, diabetes, bronchiectasis, chronic bronchitis, emphysema, cancer or chronic collagen disease
Interventions	Vaccination Type: split influenza vaccine (H3N2, B) with subviron component (H1N1) 0.5 ml intramuscular injection. Placebo: 0.5 ml intramuscular injection of physiological saline
Outcomes	Early: daily PEF readings, symptom score, daily medication for first week. Late: daily PEF readings, symptom score, daily medication for five months
Notes	The incidence of influenza was very low in Finland in the follow-up period. Sub-group analysis was performed on the early outcomes to investigate the change in peak flow in different asthma types

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	Study investigators unaware as to order of treatment group assignment (Cochrane Grade A)

Tanaka 1993

Methods	Randomisation: no details Blinding: unclear Number excluded: none? Withdrawals: 6/20 vaccine group, 8/25 placebo group discharged from hospital. Baseline characteristics: serology only Jadad score:2
Participants	Location: Minami-Fukuoka chest hospital, Japan. In-patients on asthma ward. Number and age of participants: 45 children mean age 10.5 years (SD 2.5) Asthma definition and severity: institutionalised patients with bronchial asthma (no details) Inclusion criteria: in-patients in asthma ward. Exclusion criteria: not stated
Interventions	Vaccination Type: intranasal cold-adapted recombinant trivalent influenza vaccine (H1N1, H3N2, B). Dose 0.3 ml both nostrils by nasal spray. Placebo: saline innoculation.
Outcomes	Early: "Asthma attacks", school absence. Late: Confirmed influenza (virus isolation or confirmed four-fold antibody rises with fever)
Notes	Baseline serology was similar in vaccinated and placebo groups

Tanaka 1993 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	Information not available (Cochrane Grade B)

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

Study	Reason for exclusion
Abadoglu 2004	Participants were not randomised to active treatment or control. (Age/sex matched controls were selected for the control group)
Ahmed 1997	Non-randomised before and after study
Ambrosch 1976	Mixed population of patients with rhinitis and asthma with no separate data for asthmatics
Balluch 1972	No randomisation. No separate asthma data, mixed group of allergic patients
Buchanan 2005	Comment on Bueving study
Campbell 1984	Not clearly stated as being randomised and no response from authors
Chiu 2003	Quasi-randomised as patients were alternately allocated to treatment groups
De Jongste 1984	Not randomised.
Dixon 2006	Cohort study
Kava 1987	Not stated as randomised and no response from authors.
Kim 2003	Not stated as randomised
Kramarz 2000	Not randomised
McIntosh 1977	No asthma outcomes measured.
Migueres 1987	No randomisation of vaccination in asthmatics (no control intervention)
Modlin 1977	No separate data on asthmatic patients (study of children in seven chronic disease categories)
Park 1996	No randomisation of vaccination (comparison of influenza vaccination in asthmatics without asthma symptoms or with acute asthma)

(*Continued)*

PRISMA 2005	Case Control Study (not randomised)
Sakaguchi 1994	No asthma outcomes measured.
Sugaya 1994	Self-selected treatment group (no randomisation).
Tata 2003	Not randomised.
Warshauer 1975	No randomisation of asthmatic patients.
Watanabe 2005	Not randomised

DATA AND ANALYSES

Comparison 1. Split virus or Surface Antigen vaccine v. Placebo (Benefits)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Influenza related asthma exacerbations	1		Risk Difference (M-H, Fixed, 95% CI)	Subtotals only
1.1 Number of participants with influenza related exacerbations	1	696	Risk Difference (M-H, Fixed, 95% CI)	0.01 [-0.02, 0.04]
1.2 Number of patients with any asthma exacerbation	1	696	Risk Difference (M-H, Fixed, 95% CI)	-0.04 [-0.09, 0.00]
2 Duration of influenza related asthma exacerbation (days)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3 Severity of influenza related asthma exacerbation (symptom score)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4 Difference in Symptom score during influenza positive weeks	1	40	Mean difference (Fixed, 95% CI)	0.6 [0.12, 1.08]
5 Proportion of patients with minimum important difference in total symptom score (influenza-positve weeks)	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
6 FEV1 (%predicted) during influenza positive weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Comparison 2. Split virus or Surface Antigen vaccine v. Placebo (Harms)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Patients with an exacerbation of asthma	2	4412	Risk Difference (M-H, Fixed, 95% CI)	-0.00 [-0.02, 0.02]
1.1 First-time vaccinees	2	948	Risk Difference (M-H, Fixed, 95% CI)	0.02 [-0.03, 0.07]
1.2 Repeat vaccinees	2	3464	Risk Difference (M-H, Fixed, 95% CI)	-0.01 [-0.03, 0.02]
2 Patients with a fall in PEF of over 30%	2	4252	Risk Difference (M-H, Fixed, 95% CI)	0.00 [-0.02, 0.03]
2.1 First-time vaccinees	1	194	Risk Difference (M-H, Fixed, 95% CI)	0.06 [0.01, 0.11]
2.2 Repeat vacinees	1	328	Risk Difference (M-H, Fixed, 95% CI)	0.01 [-0.01, 0.03]
2.3 Vaccination status unspecified	1	3730	Risk Difference (M-H, Fixed, 95% CI)	Not estimable
3 Fall in mean Peak Flow (% baseline) days 2-4	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4 Change in airways responsiveness			Other data	No numeric data

5 Increased nebuliser usage (days 1-3)	1		Risk Difference (M-H, Fixed, 95% CI)	Totals not selected
6 Increased use of bronchodilators following vaccination (days 1-3)	4	4924	Risk Difference (M-H, Fixed, 95% CI)	0.00 [-0.01, 0.02]
7 Hospital admission (0-14 days post-immunisation)	1		Risk Difference (M-H, Fixed, 95% CI)	Totals not selected
8 Medical consultation (0-14 days after immunisation)	3	5092	Risk Difference (M-H, Fixed, 95% CI)	0.00 [-0.01, 0.02]
9 New or increased oral steroid use (0-14 days after immunisation)	2	4419	Risk Difference (M-H, Fixed, 95% CI)	0.00 [-0.01, 0.01]
10 One or more day off school or work	2	4600	Risk Difference (M-H, Fixed, 95% CI)	Not estimable
11 Number of symptom free days in fortnight after vaccination	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
12 Change in asthma symptoms in the week following vaccination.			Other data	No numeric data

Comparison 3. Live Attenuated Cold Recombinant vaccine v. Placebo (Benefits)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All outcomes			Other data	No numeric data

Comparison 4. Live Attenuated Cold Recombinant vaccine v. Placebo (Harms)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Hospital admission for asthma exacerbation	1		Risk Difference (M-H, Fixed, 95% CI)	Totals not selected
2 Asthma exacerbations in the month after vaccination	1		Risk Difference (M-H, Fixed, 95% CI)	Totals not selected
3 Asthma exacerbations in the week following vaccination			Other data	No numeric data
4 Mean FEV1 at 2-5 days post vaccination (% predicted)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5 Numer of patients with significant fall in FEV1 (over 12%-15% or 50mls) on day 2-4	2	65	Risk Difference (M-H, Fixed, 95% CI)	0.01 [-0.12, 0.15]
6 Fall in mean FEV1 in litres (day 2-4)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

7 Number of puffs of beta-2 agonist per day (in month following vaccination)	1	Mean Difference (IV, Fixed, 95% CI)	Totals not selected
8 Morning Peak Flow of >30% below baseline at least once in the 4 weeks after vaccination	1	Risk Difference (M-H, Fixed, 95% CI)	Totals not selected

Comparison 5. Immunisation with Whole virus v. Split virus v. Subunit vaccine (Harms)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Home Peak Flow measurements before and after vaccination			Other data	No numeric data
2 Lung function measurements			Other data	No numeric data

Comparison 6. Live attenuated vaccine (intranasal) v trivalent inactivated vaccine (intramuscular). (Total study data).

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Difference in incidence of asthma exacerbation over total study period	1		% Rate difference (Fixed, 95% CI)	Totals not selected
2 Hospitalisations due to Respiratory Illness	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Days off school or work (incidence rates)	1		Rate Ratio (Fixed, 95% CI)	Totals not selected
4 Unscheduled Healthcare visits (incidence rates)	1		Rate ratio (Fixed, 95% CI)	Totals not selected
5 Children with Serious Adverse Events	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 7. Live attenuated vaccine (intranasal) v trivalent inactivated vaccine (intramuscular): (Harms)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Subjects reporting wheeze in the first 15 days	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Subjects reporting runny nose or nasal congestion in the first 15 days	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

3 Subjects reporting bronchospasm as an adverse event in first 15 days	1	Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Subjects reporting rhinitis as an adverse event in the first 15 days	1	Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Split virus or Surface Antigen vaccine v. Placebo (Benefits), Outcome 1 Influenza related asthma exacerbations.

Review: Vaccines for preventing influenza in people with asthma

Comparison: 1 Split virus or Surface Antigen vaccine v. Placebo (Benefits)

Outcome: 1 Influenza related asthma exacerbations

Study or subgroup	Treatment n/N	Control n/N	Risk Difference M-H,Fixed,95% CI	Weight	Risk Difference M-H,Fixed,95% CI
1 Number of participants with influenza related exacerbations					
Bueving 2003	20/347	17/349		100.0 %	0.01 [-0.02, 0.04]
Subtotal (95% CI)	**347**	**349**		**100.0 %**	**0.01 [-0.02, 0.04]**
Total events: 20 (Treatment), 17 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.52 (P = 0.60)					
2 Number of patients with any asthma exacerbation					
Bueving 2003	297/347	314/349		100.0 %	-0.04 [-0.09, 0.00]
Subtotal (95% CI)	**347**	**349**		**100.0 %**	**-0.04 [-0.09, 0.00]**
Total events: 297 (Treatment), 314 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.77 (P = 0.077)					

Analysis 1.2. Comparison 1 Split virus or Surface Antigen vaccine v. Placebo (Benefits), Outcome 2 Duration of influenza related asthma exacerbation (days).

Review: Vaccines for preventing influenza in people with asthma

Comparison: 1 Split virus or Surface Antigen vaccine v. Placebo (Benefits)

Outcome: 2 Duration of influenza related asthma exacerbation (days)

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Bueving 2003	24	9.2 (3.6)	18	11.2 (5.3)		-2.00 [-4.84, 0.84]

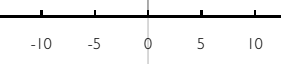
Analysis 1.3. Comparison 1 Split virus or Surface Antigen vaccine v. Placebo (Benefits), Outcome 3 Severity of influenza related asthma exacerbation (symptom score).

Review: Vaccines for preventing influenza in people with asthma

Comparison: 1 Split virus or Surface Antigen vaccine v. Placebo (Benefits)

Outcome: 3 Severity of influenza related asthma exacerbation (symptom score)

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Bueving 2003	24	4.7 (2.7)	18	6.4 (3.1)		-1.70 [-3.49, 0.09]



Analysis 1.4. Comparison 1 Split virus or Surface Antigen vaccine v. Placebo (Benefits), Outcome 4 Difference in Symptom score during influenza positive weeks.

Review: Vaccines for preventing influenza in people with asthma

Comparison: 1 Split virus or Surface Antigen vaccine v. Placebo (Benefits)

Outcome: 4 Difference in Symptom score during influenza positive weeks

Study or subgroup	Vaccinated N	Control N	Mean difference (SE)	Mean difference IV,Fixed,95% CI	Weight	Mean difference IV,Fixed,95% CI
Bueving 2003	21	19	0.6 (0.247)		100.0 %	0.60 [0.12, 1.08]
Total (95% CI)					**100.0 %**	**0.60 [0.12, 1.08]**

Heterogeneity: not applicable

Test for overall effect: Z = 2.43 (P = 0.015)

Test for subgroup differences: Not applicable

Analysis 1.5. Comparison 1 Split virus or Surface Antigen vaccine v. Placebo (Benefits), Outcome 5 Proportion of patients with minimum important difference in total symptom score (influenza-positve weeks).

Review: Vaccines for preventing influenza in people with asthma

Comparison: 1 Split virus or Surface Antigen vaccine v. Placebo (Benefits)

Outcome: 5 Proportion of patients with minimum important difference in total symptom score (influenza-positve weeks)

Study or subgroup	Vaccinated n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
Bueving 2003	10/21	13/19		0.42 [0.12, 1.53]

Analysis 1.6. Comparison 1 Split virus or Surface Antigen vaccine v. Placebo (Benefits), Outcome 6 FEV1 (%predicted) during influenza positive weeks.

Review: Vaccines for preventing influenza in people with asthma

Comparison: 1 Split virus or Surface Antigen vaccine v. Placebo (Benefits)

Outcome: 6 FEV1 (%predicted) during influenza positive weeks

Study or subgroup	Vaccinated N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Bueving 2003	21	89 (22)	20	80 (20)		9.00 [-3.86, 21.86]

Analysis 2.1. Comparison 2 Split virus or Surface Antigen vaccine v. Placebo (Harms), Outcome 1 Patients with an exacerbation of asthma.

Review: Vaccines for preventing influenza in people with asthma

Comparison: 2 Split virus or Surface Antigen vaccine v. Placebo (Harms)

Outcome: 1 Patients with an exacerbation of asthma

Study or subgroup	Treatment n/N	Control n/N	Risk Difference M-H,Fixed,95% CI	Weight	Risk Difference M-H,Fixed,95% CI
1 First-time vaccinees					
Castro 2001	113/377	111/377		17.1 %	0.01 [-0.06, 0.07]
Nicholson 1998	9/97	1/97		4.4 %	0.08 [0.02, 0.14]
Subtotal (95% CI)	**474**	**474**		**21.5 %**	**0.02 [-0.03, 0.07]**
Total events: 122 (Treatment), 112 (Control)					
Heterogeneity: Chi^2 = 4.10, df = 1 (P = 0.04); I^2 =76%					
Test for overall effect: Z = 0.77 (P = 0.44)					
2 Repeat vaccinees					
Castro 2001	1283/1568	1296/1568		71.1 %	-0.01 [-0.04, 0.02]
Nicholson 1998	2/164	2/164		7.4 %	0.0 [-0.02, 0.02]

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Study or subgroup	Treatment n/N	Control n/N	Risk Difference M-H,Fixed,95% CI	Weight	Risk Difference M-H,Fixed,95% CI
Subtotal (95% CI)	**1732**	**1732**		**78.5 %**	**-0.01 [-0.03, 0.02]**
Total events: 1285 (Treatment), 1298 (Control)					
Heterogeneity: Chi^2 = 0.39, df = 1 (P = 0.53); I^2 =0.0%					
Test for overall effect: Z = 0.60 (P = 0.55)					
Total (95% CI)	**2206**	**2206**		**100.0 %**	**0.00 [-0.02, 0.02]**
Total events: 1407 (Treatment), 1410 (Control)					
Heterogeneity: Chi^2 = 7.53, df = 3 (P = 0.06); I^2 =60%					
Test for overall effect: Z = 0.12 (P = 0.90)					

Analysis 2.2. Comparison 2 Split virus or Surface Antigen vaccine v. Placebo (Harms), Outcome 2 Patients with a fall in PEF of over 30%.

Review: Vaccines for preventing influenza in people with asthma

Comparison: 2 Split virus or Surface Antigen vaccine v. Placebo (Harms)

Outcome: 2 Patients with a fall in PEF of over 30%

Study or subgroup	Treatment n/N	Control n/N	Risk Difference M-H,Fixed,95% CI	Weight	Risk Difference M-H,Fixed,95% CI
1 First-time vaccinees					
Nicholson 1998	6/97	0/97		4.6 %	0.06 [0.01, 0.11]
Subtotal (95% CI)	**97**	**97**		**4.6 %**	**0.06 [0.01, 0.11]**
Total events: 6 (Treatment), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.37 (P = 0.018)					
2 Repeat vaccinees					
Nicholson 1998	2/164	0/164		7.7 %	0.01 [-0.01, 0.03]
Subtotal (95% CI)	**164**	**164**		**7.7 %**	**0.01 [-0.01, 0.03]**
Total events: 2 (Treatment), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.17 (P = 0.24)					

(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	Treatment n/N	Control n/N	Risk Difference M-H,Fixed,95% CI	Weight	Risk Difference M-H,Fixed,95% CI
3 Vaccination status unspecified					
Castro 2001	311/1865	310/1865		87.7 %	0.00 [-0.02, 0.02]
Subtotal (95% CI)	**1865**	**1865**		**87.7 %**	**0.00 [-0.02, 0.02]**
Total events: 311 (Treatment), 310 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.04 (P = 0.96)					
Total (95% CI)	**2126**	**2126**		**100.0 %**	**0.00 [-0.02, 0.03]**
Total events: 319 (Treatment), 310 (Control)					
Heterogeneity: Chi^2 = 5.53, df = 2 (P = 0.06); I^2 =64%					
Test for overall effect: Z = 0.39 (P = 0.70)					

Analysis 2.3. Comparison 2 Split virus or Surface Antigen vaccine v. Placebo (Harms), Outcome 3 Fall in mean Peak Flow (% baseline) days 2-4.

Review: Vaccines for preventing influenza in people with asthma

Comparison: 2 Split virus or Surface Antigen vaccine v. Placebo (Harms)

Outcome: 3 Fall in mean Peak Flow (% baseline) days 2-4

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Nicholson 1998	256	0.78 (9)	260	-0.51 (7.3)		1.29 [-0.13, 2.71]
Stenius 1986	161	3 (7)	157	3 (8)		0.0 [-1.65, 1.65]
Subtotal (95% CI)	**0**		**0**			**0.0 [0.0, 0.0]**
Heterogeneity: Chi^2 = 0.0, df = 0 (P<0.00001); I^2 =0.0%						
Test for overall effect: Z = 0.0 (P < 0.00001)						
Test for subgroup differences: Not applicable						

Analysis 2.4. Comparison 2 Split virus or Surface Antigen vaccine v. Placebo (Harms), Outcome 4 Change in airways responsiveness.

Change in airways responsiveness

Study	
Kut 1999	No significant change in PC20 following either placebo or vaccine. PC20 (SD) in the placebo group was 7.02 (9.3) before challenge and 7.3 (3.6) after 24 hours. In the vaccine group PC20 was 9.5(10.6) before vaccine and 9.8(9.3) afterwards. (P>0.05)
Reid 1998	No significant difference found in placebo group (n=5) or vaccination group (n=17) in either mean PD20 or mean FEV1 (tested by analysis of variance ANOVA). No individual patient in either group showed a change of PD20 of more than two-fold
Sener 1999	No significant difference between placebo and vaccine in PD20 at 2 weeks. Vaccine 2.96(SD 3.2) and placebo 2.76 (SD 2.91)

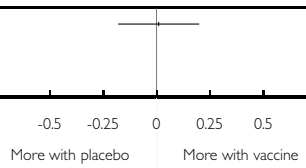
Analysis 2.5. Comparison 2 Split virus or Surface Antigen vaccine v. Placebo (Harms), Outcome 5 Increased nebuliser usage (days 1-3).

Review: Vaccines for preventing influenza in people with asthma

Comparison: 2 Split virus or Surface Antigen vaccine v. Placebo (Harms)

Outcome: 5 Increased nebuliser usage (days 1-3)

Study or subgroup	Treatment n/N	Control n/N	Risk Difference M-H,Fixed,95% CI	Risk Difference M-H,Fixed,95% CI
Nicholson 1998	7/33	7/35		0.01 [-0.18, 0.20]



Analysis 2.6. Comparison 2 Split virus or Surface Antigen vaccine v. Placebo (Harms), Outcome 6 Increased use of bronchodilators following vaccination (days 1-3).

Review: Vaccines for preventing influenza in people with asthma

Comparison: 2 Split virus or Surface Antigen vaccine v. Placebo (Harms)

Outcome: 6 Increased use of bronchodilators following vaccination (days 1-3)

Study or subgroup	Treatment n/N	Control n/N	Risk Difference M-H,Fixed,95% CI	Weight	Risk Difference M-H,Fixed,95% CI
Bueving 2003	234/347	227/349		14.1 %	0.02 [-0.05, 0.09]
Castro 2001	113/1858	121/1858		75.5 %	0.00 [-0.02, 0.01]
Nicholson 1998	52/228	48/236		9.4 %	0.02 [-0.05, 0.10]
Sener 1999	0/24	0/24		1.0 %	0.0 [-0.08, 0.08]
Total (95% CI)	**2457**	**2467**		**100.0 %**	**0.00 [-0.01, 0.02]**

Total events: 399 (Treatment), 396 (Control)

Heterogeneity: Chi^2 = 1.42, df = 3 (P = 0.70); I^2 =0.0%

Test for overall effect: Z = 0.28 (P = 0.78)

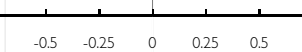
Analysis 2.7. Comparison 2 Split virus or Surface Antigen vaccine v. Placebo (Harms), Outcome 7 Hospital admission (0-14 days post-immunisation).

Review: Vaccines for preventing influenza in people with asthma

Comparison: 2 Split virus or Surface Antigen vaccine v. Placebo (Harms)

Outcome: 7 Hospital admission (0-14 days post-immunisation)

Study or subgroup	Treatment n/N	Control n/N	Risk Difference M-H,Fixed,95% CI	Risk Difference M-H,Fixed,95% CI
Nicholson 1998	1/256	1/256		0.0 [-0.01, 0.01]



Analysis 2.8. Comparison 2 Split virus or Surface Antigen vaccine v. Placebo (Harms), Outcome 8 Medical consultation (0-14 days after immunisation).

Review: Vaccines for preventing influenza in people with asthma

Comparison: 2 Split virus or Surface Antigen vaccine v. Placebo (Harms)

Outcome: 8 Medical consultation (0-14 days after immunisation)

Study or subgroup	Treatment n/N	Control n/N	Risk Difference M-H,Fixed,95% CI	Weight	Risk Difference M-H,Fixed,95% CI
Bueving 2003	4/347	3/349		13.7 %	0.00 [-0.01, 0.02]
Castro 2001	107/1952	100/1952		76.7 %	0.00 [-0.01, 0.02]
Nicholson 1998	10/244	7/248		9.7 %	0.01 [-0.02, 0.05]
Total (95% CI)	**2543**	**2549**		**100.0 %**	**0.00 [-0.01, 0.02]**

Total events: 121 (Treatment), 110 (Control)

Heterogeneity: $Chi^2 = 0.31$, df = 2 (P = 0.86); $I^2 = 0.0\%$

Test for overall effect: Z = 0.75 (P = 0.45)

Analysis 2.9. Comparison 2 Split virus or Surface Antigen vaccine v. Placebo (Harms), Outcome 9 New or increased oral steroid use (0-14 days after immunisation).

Review: Vaccines for preventing influenza in people with asthma

Comparison: 2 Split virus or Surface Antigen vaccine v. Placebo (Harms)

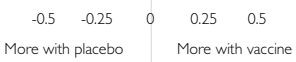
Outcome: 9 New or increased oral steroid use (0-14 days after immunisation)

Study or subgroup	Treatment n/N	Control n/N	Risk Difference M-H,Fixed,95% CI	Weight	Risk Difference M-H,Fixed,95% CI
Castro 2001	103/1952	100/1952		88.3 %	0.00 [-0.01, 0.02]
Nicholson 1998	7/257	5/258		11.7 %	0.01 [-0.02, 0.03]
Total (95% CI)	**2209**	**2210**		**100.0 %**	**0.00 [-0.01, 0.01]**

Total events: 110 (Treatment), 105 (Control)

Heterogeneity: $Chi^2 = 0.19$, df = 1 (P = 0.67); $I^2 = 0.0\%$

Test for overall effect: Z = 0.35 (P = 0.73)



Analysis 2.10. Comparison 2 Split virus or Surface Antigen vaccine v. Placebo (Harms), Outcome 10 One or more day off school or work.

Review: Vaccines for preventing influenza in people with asthma

Comparison: 2 Split virus or Surface Antigen vaccine v. Placebo (Harms)

Outcome: 10 One or more day off school or work

Study or subgroup	Treatment n/N	Control n/N	Risk Difference M-H,Fixed,95% CI	Weight	Risk Difference M-H,Fixed,95% CI
Bueving 2003	19/347	21/349		15.1 %	-0.01 [-0.04, 0.03]
Castro 2001	131/1952	131/1952		84.9 %	0.0 [-0.02, 0.02]
Total (95% CI)	**2299**	**2301**		**100.0 %**	**0.00 [-0.02, 0.01]**

Total events: 150 (Treatment), 152 (Control)

Heterogeneity: $Chi^2 = 0.08$, df = 1 (P = 0.78); $I^2 = 0.0\%$

Test for overall effect: Z = 0.11 (P = 0.91)

Analysis 2.11. Comparison 2 Split virus or Surface Antigen vaccine v. Placebo (Harms), Outcome 11 Number of symptom free days in fortnight after vaccination.

Review: Vaccines for preventing influenza in people with asthma

Comparison: 2 Split virus or Surface Antigen vaccine v. Placebo (Harms)

Outcome: 11 Number of symptom free days in fortnight after vaccination

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Castro 2001	1851	10.4 (4.7)	1851	10.4 (4.7)		0.0 [-0.30, 0.30]

Analysis 2.12. Comparison 2 Split virus or Surface Antigen vaccine v. Placebo (Harms), Outcome 12 Change in asthma symptoms in the week following vaccination..

Change in asthma symptoms in the week following vaccination.

Study	
Govaert 1992	No adverse reactions on asthma symptoms reported from any of the 14 asthmatics immunised with split-virus vaccine or the 11 astmatics given placebo. (Communication from author)
Hahn 1980	No significant deterioration in home Peak Flow measurement in the split vaccine (25 patients), subunit vaccine (25 patients) or placebo group (16 patients) in the two weeks following vaccination. No numerical data given
Sener 1999	No significant difference in symptom scores in the week after vaccine. Placebo mean score 4.66 (SD 7.3), vaccine mean score 4.92 (SD 7.56)
Stenius 1986	Similar in the vaccine and placebo groups. No numerical data provided

Analysis 4.1. Comparison 4 Live Attenuated Cold Recombinant vaccine v. Placebo (Harms), Outcome 1 Hospital admission for asthma exacerbation.

Review: Vaccines for preventing influenza in people with asthma

Comparison: 4 Live Attenuated Cold Recombinant vaccine v. Placebo (Harms)

Outcome: 1 Hospital admission for asthma exacerbation

Study or subgroup	Treatment n/N	Control n/N	Risk Difference M-H,Fixed,95% CI	Risk Difference M-H,Fixed,95% CI
Atmar 1989	0/11	1/6		-0.17 [-0.49, 0.16]

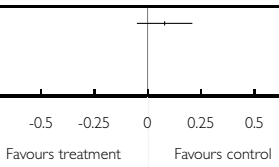
Analysis 4.2. Comparison 4 Live Attenuated Cold Recombinant vaccine v. Placebo (Harms), Outcome 2 Asthma exacerbations in the month after vaccination.

Review: Vaccines for preventing influenza in people with asthma

Comparison: 4 Live Attenuated Cold Recombinant vaccine v. Placebo (Harms)

Outcome: 2 Asthma exacerbations in the month after vaccination

Study or subgroup	Treatment n/N	Control n/N	Risk Difference M-H,Fixed,95% CI	Risk Difference M-H,Fixed,95% CI
Redding 2002	2/24	0/24		0.08 [-0.05, 0.21]



Analysis 4.3. Comparison 4 Live Attenuated Cold Recombinant vaccine v. Placebo (Harms), Outcome 3 Asthma exacerbations in the week following vaccination.

Asthma exacerbations in the week following vaccination

Study	
Miyazaki 1993	No asthma attacks were apparent following vaccination. Evaluation was made difficult by an Adenovirus outbreak during the study period. No defintion of asthma attack provided by the authors
Tanaka 1993	No asthma attacks were observed following vaccination (20 patients given CR vaccine and 25 given placebo). No defintion of asthma attack provided by the authors

Analysis 4.4. Comparison 4 Live Attenuated Cold Recombinant vaccine v. Placebo (Harms), Outcome 4 Mean FEV1 at 2-5 days post vaccination (% predicted).

Review: Vaccines for preventing influenza in people with asthma

Comparison: 4 Live Attenuated Cold Recombinant vaccine v. Placebo (Harms)

Outcome: 4 Mean FEV1 at 2-5 days post vaccination (% predicted)

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Redding 2002	24	75.3 (16.8)	24	76.4 (12.2)		-1.10 [-9.41, 7.21]

Analysis 4.5. Comparison 4 Live Attenuated Cold Recombinant vaccine v. Placebo (Harms), Outcome 5 Numer of patients with significant fall in FEV1 (over 12%-15% or 50mls) on day 2-4.

Review: Vaccines for preventing influenza in people with asthma

Comparison: 4 Live Attenuated Cold Recombinant vaccine v. Placebo (Harms)

Outcome: 5 Numer of patients with significant fall in FEV1 (over 12%-15% or 50mls) on day 2-4

Study or subgroup	Treatment n/N	Control n/N	Risk Difference M-H,Fixed,95% CI	Weight	Risk Difference M-H,Fixed,95% CI
Atmar 1989	1/11	1/6		24.4 %	-0.08 [-0.42, 0.27]
Redding 2002	2/24	1/24		75.6 %	0.04 [-0.09, 0.18]
Total (95% CI)	**35**	**30**		**100.0 %**	**0.01 [-0.12, 0.15]**

Total events: 3 (Treatment), 2 (Control)

Heterogeneity: Chi^2 = 0.43, df = 1 (P = 0.51); I^2 =0.0%

Test for overall effect: Z = 0.19 (P = 0.85)

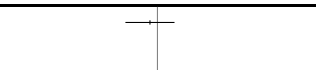
Analysis 4.6. Comparison 4 Live Attenuated Cold Recombinant vaccine v. Placebo (Harms), Outcome 6 Fall in mean FEV1 in litres (day 2-4).

Review: Vaccines for preventing influenza in people with asthma

Comparison: 4 Live Attenuated Cold Recombinant vaccine v. Placebo (Harms)

Outcome: 6 Fall in mean FEV1 in litres (day 2-4)

Study or subgroup	Vaccine N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Atmar 1989	11	-0.03 (0.19)	6	0.04 (0.25)		-0.07 [-0.30, 0.16]



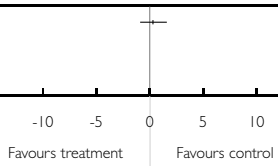
Analysis 4.7. Comparison 4 Live Attenuated Cold Recombinant vaccine v. Placebo (Harms), Outcome 7 Number of puffs of beta-2 agonist per day (in month following vaccination).

Review: Vaccines for preventing influenza in people with asthma

Comparison: 4 Live Attenuated Cold Recombinant vaccine v. Placebo (Harms)

Outcome: 7 Number of puffs of beta-2 agonist per day (in month following vaccination)

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Redding 2002	24	2.8 (2.4)	24	2.5 (2)		0.30 [-0.95, 1.55]



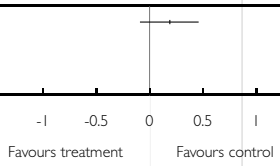
Analysis 4.8. Comparison 4 Live Attenuated Cold Recombinant vaccine v. Placebo (Harms), Outcome 8 Morning Peak Flow of >30% below baseline at least once in the 4 weeks after vaccination.

Review: Vaccines for preventing influenza in people with asthma

Comparison: 4 Live Attenuated Cold Recombinant vaccine v. Placebo (Harms)

Outcome: 8 Morning Peak Flow of >30% below baseline at least once in the 4 weeks after vaccination

Study or subgroup	Treatment n/N	Control n/N	Risk Difference M-H,Fixed,95% CI	Risk Difference M-H,Fixed,95% CI
Redding 2002	17/24	12/23		0.19 [-0.09, 0.46]



Analysis 5.1. Comparison 5 Immunisation with Whole virus v. Split virus v. Subunit vaccine (Harms), Outcome 1 Home Peak Flow measurements before and after vaccination.

Home Peak Flow measurements before and after vaccination

Study	
Ortwein 1987	No significant differences found in home Peak Flow measurements in the three days following vaccination in any of the vaccine groups individually or together. No numerical data provided in the paper

Analysis 5.2. Comparison 5 Immunisation with Whole virus v. Split virus v. Subunit vaccine (Harms), Outcome 2 Lung function measurements.

Lung function measurements

Study	
Ortwein 1987	No deterioration in Lung Function measured in the laboratory in the 3 days following immunisation (either no change or small improvements seen.) No numerical data provided

Analysis 6.1. Comparison 6 Live attenuated vaccine (intranasal) v trivalent inactivated vaccine (intramuscular). (Total study data)., Outcome 1 Difference in incidence of asthma exacerbation over total study period.

Review: Vaccines for preventing influenza in people with asthma

Comparison: 6 Live attenuated vaccine (intranasal) v trivalent inactivated vaccine (intramuscular). (Total study data).

Outcome: 1 Difference in incidence of asthma exacerbation over total study period

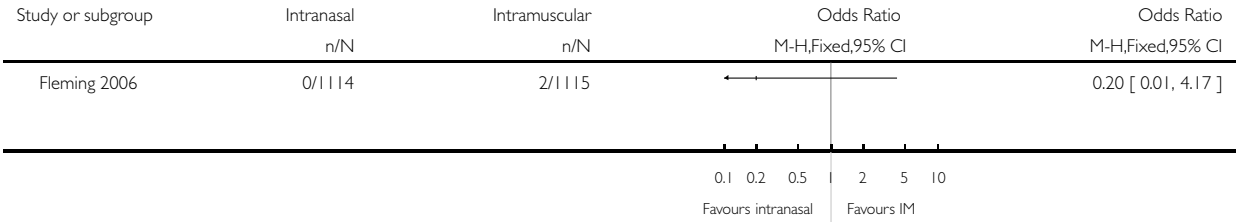
Study or subgroup	Intranasal N	IM N	% Rate difference (SE)	% Rate difference IV,Fixed,95% CI	% Rate difference IV,Fixed,95% CI
Fleming 2006	1114	1115	1.6 (1.9388)		1.60 [-2.20, 5.40]

Analysis 6.2. Comparison 6 Live attenuated vaccine (intranasal) v trivalent inactivated vaccine (intramuscular). (Total study data)., Outcome 2 Hospitalisations due to Respiratory Illness.

Review: Vaccines for preventing influenza in people with asthma

Comparison: 6 Live attenuated vaccine (intranasal) v trivalent inactivated vaccine (intramuscular). (Total study data).

Outcome: 2 Hospitalisations due to Respiratory Illness

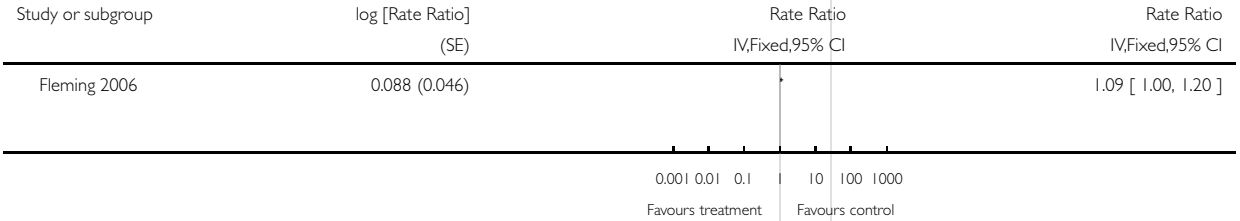


Analysis 6.3. Comparison 6 Live attenuated vaccine (intranasal) v trivalent inactivated vaccine (intramuscular). (Total study data)., Outcome 3 Days off school or work (incidence rates).

Review: Vaccines for preventing influenza in people with asthma

Comparison: 6 Live attenuated vaccine (intranasal) v trivalent inactivated vaccine (intramuscular). (Total study data).

Outcome: 3 Days off school or work (incidence rates)

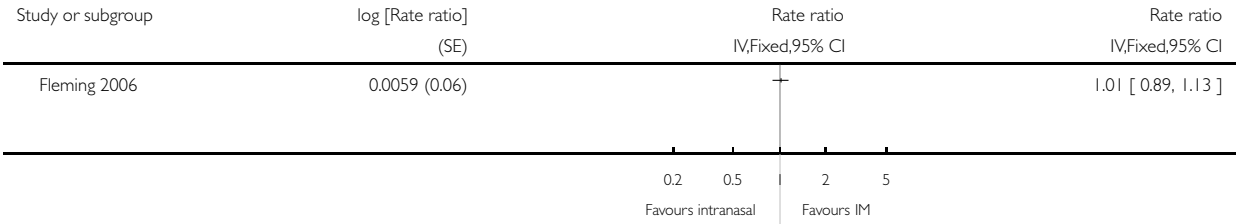


Analysis 6.4. Comparison 6 Live attenuated vaccine (intranasal) v trivalent inactivated vaccine (intramuscular). (Total study data)., Outcome 4 Unscheduled Healthcare visits (incidence rates).

Review: Vaccines for preventing influenza in people with asthma

Comparison: 6 Live attenuated vaccine (intranasal) v trivalent inactivated vaccine (intramuscular). (Total study data).

Outcome: 4 Unscheduled Healthcare visits (incidence rates)

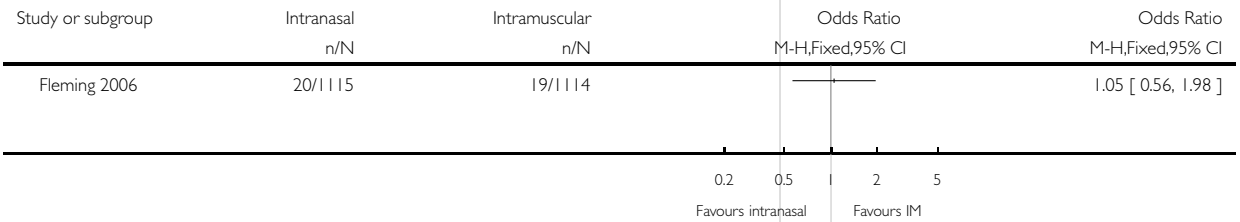


Analysis 6.5. Comparison 6 Live attenuated vaccine (intranasal) v trivalent inactivated vaccine (intramuscular). (Total study data)., Outcome 5 Children with Serious Adverse Events.

Review: Vaccines for preventing influenza in people with asthma

Comparison: 6 Live attenuated vaccine (intranasal) v trivalent inactivated vaccine (intramuscular). (Total study data).

Outcome: 5 Children with Serious Adverse Events

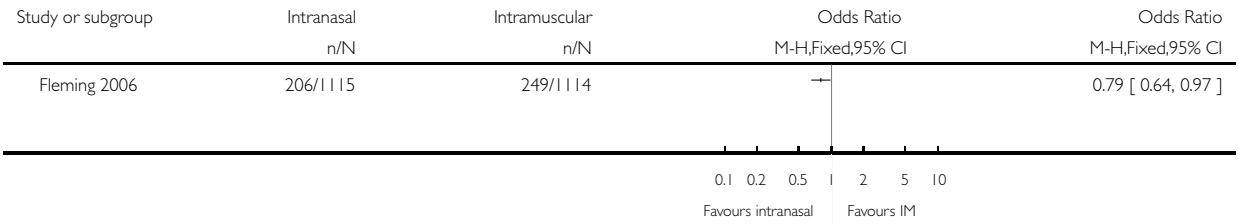


Analysis 7.1. Comparison 7 Live attenuated vaccine (intranasal) v trivalent inactivated vaccine (intramuscular): (Harms), Outcome 1 Subjects reporting wheeze in the first 15 days.

Review: Vaccines for preventing influenza in people with asthma

Comparison: 7 Live attenuated vaccine (intranasal) v trivalent inactivated vaccine (intramuscular): (Harms)

Outcome: 1 Subjects reporting wheeze in the first 15 days

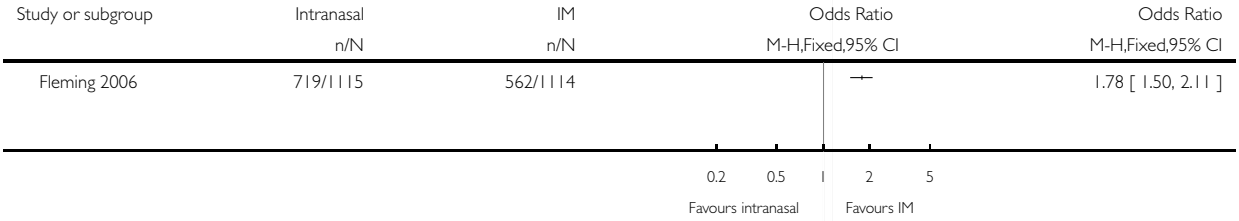


Analysis 7.2. Comparison 7 Live attenuated vaccine (intranasal) v trivalent inactivated vaccine (intramuscular): (Harms), Outcome 2 Subjects reporting runny nose or nasal congestion in the first 15 days.

Review: Vaccines for preventing influenza in people with asthma

Comparison: 7 Live attenuated vaccine (intranasal) v trivalent inactivated vaccine (intramuscular): (Harms)

Outcome: 2 Subjects reporting runny nose or nasal congestion in the first 15 days

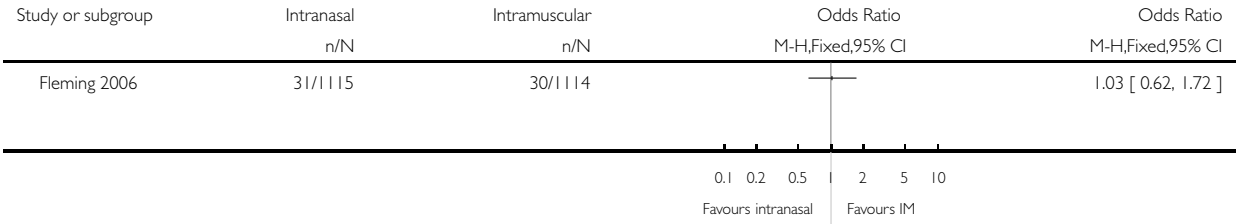


Analysis 7.3. Comparison 7 Live attenuated vaccine (intranasal) v trivalent inactivated vaccine (intramuscular): (Harms), Outcome 3 Subjects reporting bronchospasm as an adverse event in first 15 days.

Review: Vaccines for preventing influenza in people with asthma

Comparison: 7 Live attenuated vaccine (intranasal) v trivalent inactivated vaccine (intramuscular): (Harms)

Outcome: 3 Subjects reporting bronchospasm as an adverse event in first 15 days

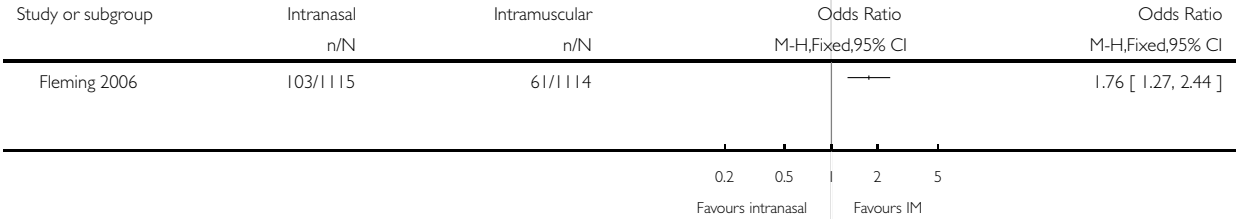


Analysis 7.4. Comparison 7 Live attenuated vaccine (intranasal) v trivalent inactivated vaccine (intramuscular): (Harms), Outcome 4 Subjects reporting rhinitis as an adverse event in the first 15 days.

Review: Vaccines for preventing influenza in people with asthma

Comparison: 7 Live attenuated vaccine (intranasal) v trivalent inactivated vaccine (intramuscular): (Harms)

Outcome: 4 Subjects reporting rhinitis as an adverse event in the first 15 days



WHAT'S NEW

Last assessed as up-to-date: 17 February 2008.

Date	Event	Description
4 December 2008	Amended	Search methods edited. Search dates corrected.
1 September 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 1, 1997

Review first published: Issue 3, 1998

Date	Event	Description
18 February 2008	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Christopher Cates (CJC) had the idea of carrying out the review and wrote the protocol in conjunction with Tom Jefferson (TOJ) and Brian Rowe (BR). Studies for inclusion were assessed by CJC and TOJ and quality scoring was also carried out by the same authors. In the first update of the review CJC and Anna Bara assessed the new studies for inclusion and quality, and for the 2007 update CJC and Toby Lasserson assessed the new studies. CJC wrote and revised the review with assistance and advice from TOJ and BR. CJC is the guarantor of the review.

DECLARATIONS OF INTEREST

None. The authors have not represented the producers of these vaccine products. CJC acted in an advisory capacity in the design of one of the studies (Bueving 2003).

SOURCES OF SUPPORT

Internal sources

- NHS Executive (North Thames), UK.
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- Canada Institute of Health Research (CIHR), Ottawa, Canada.

INDEX TERMS

Medical Subject Headings (MeSH)

Asthma [*complications]; Influenza Vaccines [*therapeutic use]; Influenza, Human [complications; *prevention & control]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Child; Humans