Cochrane Library

Cochrane Database of Systematic Reviews

Influenza vaccines for preventing acute otitis media in infants and children (Review)

Norhayati MN, Ho JJ, Azman MY

Norhayati MN, Ho JJ, Azman MY.
Influenza vaccines for preventing acute otitis media in infants and children.
Cochrane Database of Systematic Reviews 2017, Issue 10. Art. No.: CD010089.
DOI: 10.1002/14651858.CD010089.pub3.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Influenza vaccines for preventing acute otitis media in infants and children

Mohd N Norhayati[1], Jacqueline J Ho[2], Mohd Y Azman[3]

[1]Department of Family Medicine, Universiti Sains Malaysia, Kubang Kerian, Malaysia. [2]Department of Paediatrics, Penang Medical College, Penang, Malaysia. [3]Raja Perempuan Zainab II Hospital, Kota Bharu, Malaysia

Contact address: Mohd N Norhayati, Department of Family Medicine, Universiti Sains Malaysia, School of Medical Sciences, Health Campus, Kubang Kerian, Kelantan, 16150, Malaysia. hayatikk@usm.my, drnorhayati_mn@yahoo.com.

Editorial group: Cochrane Acute Respiratory Infections Group.
Publication status and date: New search for studies and content updated (no change to conclusions), comment added to review, published in Issue 10, 2017.

Citation: Norhayati MN, Ho JJ, Azman MY. Influenza vaccines for preventing acute otitis media in infants and children. *Cochrane Database of Systematic Reviews* 2017, Issue 10. Art. No.: CD010089. DOI: 10.1002/14651858.CD010089.pub3.

ABSTRACT

Background

Acute otitis media (AOM) is one of the most common infectious diseases in children. It has been reported that 64% of infants have an episode of AOM by the age of six months and 86% by one year. Although most cases of AOM are due to bacterial infection, it is commonly triggered by a viral infection. In most children AOM is self limiting, but it does carry a risk of complications. Since antibiotic treatment increases the risk of antibiotic resistance, influenza vaccines might be an effective way of reducing this risk by preventing the development of AOM.

Objectives

To assess the effectiveness of influenza vaccine in reducing the occurrence of acute otitis media in infants and children.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, CINAHL, LILACS, Web of Science, the WHO International Clinical Trials Registry Platform, and ClinicalTrials.gov (15 February 2017). We also searched the reference lists of included studies to identify any additional trials.

Selection criteria

Randomised controlled trials comparing influenza vaccine with placebo or no treatment in infants and children aged younger than six years. We included children of either sex and of any ethnicity, with or without a history of recurrent AOM.

Data collection and analysis

Two review authors independently screened studies, assessed trial quality, and extracted data. We performed statistical analyses using the random-effects and fixed-effect models and expressed the results as risk ratio (RR), risk difference (RD), and number needed to treat for an additional beneficial outcome (NNTB) for dichotomous outcomes, with 95% confidence intervals (CI).

Main results

We included 11 trials (6 trials in high-income countries and 5 multicentre trials in high-, middle-, and low-income countries) involving 17,123 children aged 6 months to 6 years. Eight trials recruited participants from a healthcare setting. Ten trials (and all four trials that contributed to the primary outcome) declared funding from vaccine manufacturers. Four trials reported adequate allocation concealment, and 10 trials reported adequate blinding of participants and personnel. Attrition was low for eight trials included in the analysis.

The primary outcome showed a small reduction in at least one episode of AOM over at least six months of follow-up (4 trials, 3134 children; RR 0.84, 95% CI 0.69 to 1.02; RD -0.04, 95% CI -0.08 to -0.00; NNTB 25, 95% CI 12.5 to 100; low-quality evidence).

The subgroup analyses (i.e. number of courses and types of vaccine administered) showed no differences.

There was a reduction in the use of antibiotics in vaccinated children (2 trials, 1223 children; RR 0.70, 95% CI 0.59 to 0.83; RD -0.11, 95% CI -0.16 to -0.06; moderate-quality evidence).

We were unable to demonstrate whether there was any difference in the utilisation of health care. The use of influenza vaccine resulted in a significant increase in fever (7 trials, 10,615 children; RR 1.15, 95% CI 1.06 to 1.24; RD 0.02, 95% CI 0.00 to 0.04; low-quality evidence), rhinorrhoea (6 trials, 10,563 children; RR 1.17, 95% CI 1.07 to 1.29; RD 0.09, 95% CI 0.01 to 0.16; low-quality evidence), but no difference in pharyngitis. No major adverse events were reported.

Differing from the protocol, the original publication of the review included a subgroup analysis of AOM episodes by season, and the secondary outcome 'types of influenza vaccine' was changed to a subgroup analysis. For this update, we removed the subgroup analyses for trial setting, season, and utilisation of health care due to the small number of trials involved. We removed Belshe 2000 from primary and secondary outcomes (courses of vaccine and types of vaccine) because it reported episodes of AOM per person. We did not perform a subgroup analysis by type of adverse event. We have reported each type of adverse event as a separate analysis.

Authors' conclusions

Influenza vaccine results in a small reduction in AOM. The observed reduction in the use of antibiotics needs to be considered in light of current recommended practices aimed at avoiding antibiotic overuse. Safety data from these trials were limited. The benefits may not justify the use of influenza vaccine without taking into account the vaccine efficacy in reducing influenza and safety data. We judged the quality of the evidence to be low to moderate. Additional research is needed.

PLAIN LANGUAGE SUMMARY

Influenza vaccine for preventing acute otitis media (middle ear infection)

Review question

We reviewed the effect of influenza vaccine on preventing acute otitis media (AOM) in infants and children.

Background

Acute otitis media is one of the most common infectious diseases in infants and preschool children. Symptoms include ear pain and fever, but it may also cause hearing loss due to eardrum perforation or fluid accumulation in the middle ear. Acute otitis media is usually bacterial in origin and is often treated with antibiotics, which may carry the risk of antibiotic resistance. Even so, AOM is often preceded by viral infection, such as influenza. Preventing viral infections might prevent AOM. We therefore investigated whether influenza vaccines might reduce the occurrence of AOM in infants and children.

Study characteristics

The evidence is current to 15 February 2017. We selected randomised controlled trials comparing influenza vaccine with placebo or no treatment in infants and children aged six months to six years, with or without a history of previous episodes of AOM. We included 11 trials involving 17,123 children. Ten out of 11 trials were funded by vaccine manufacturers.

Key results

We found a 4% reduction in AOM and about an 11% reduction in the number of antibiotic prescriptions. There was no difference in the number of courses or types of vaccine administered between those who were vaccinated and those who were unvaccinated. Influenza vaccine side effects included an increase in fever, runny nose, and drowsiness. It remains uncertain whether the influenza vaccine reduced visits or admissions to healthcare facilities. Data were insufficient to show that this benefit might be balanced against more serious or rarer side effects from the vaccine.

Although we observed a reduction in antibiotic usage, this impact is uncertain because the current practice is to avoid overuse of antibiotics. Coupled with other vaccine safety concerns, the use of influenza vaccine to reduce AOM is not yet justified, and additional research is needed.

Quality of the evidence

The overall quality of the evidence was low to moderate.

Summary of findings for the main comparison. Influenza vaccine compared to control for preventing acute otitis media in infants and children

Influenza vaccine compared to control for preventing acute otitis media in infants and children

Patient or population: infants and children
Setting: health care and day care
Intervention: influenza vaccine
Comparison: control

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with control	Risk with influenza vaccine				
At least 1 episode of acute otitis media	Study population		RR 0.84 (0.69 to 1.02)	3134 (4 RCTs)	⊕⊕⊖⊖ LOW[1,2]	The basis for the assumed risk is the mean risk in the control group across the included studies. There was moderate unexplained inconsistency across the studies. We downgraded for inconsistency. The effect estimates were all in the same direction, but there was uncertainty in the confidence of the effect estimate.
	292 per 1000	245 per 1000 (201 to 298)				
Courses of antibiotics	Study population		RR 0.70 (0.59 to 0.83)	1223 (2 RCTs)	⊕⊕⊕⊖ MODERATE[1]	Assumed risk calculated from the mean risk across the control groups of the 2 included studies
	362 per 1000	254 per 1000 (214 to 301)				
Fever	Study population		RR 1.15 (1.06 to 1.24)	10,615 (7 RCTs)	⊕⊕⊖⊖ LOW[1,2,4]	Assumed risk calculated from the mean risk across the control groups of the 7 included studies
	174 per 1000	200 per 1000 (184 to 215)				
Rhinorrhoea	Study population		RR 1.17 (1.07 to 1.29)	10,563 (6 RCTs)	⊕⊕⊖⊖ LOW[1,2,4]	Assumed risk calculated from the mean risk across the control groups of the 6 included studies
	424 per 1000	496 per 1000 (453 to 546)				
Pharyngitis	Study population		RR 1.00 (0.80 to 1.25)	4429 (3 RCTs)	⊕⊕⊖⊖ LOW[1,2,4]	Assumed risk calculated from the mean risk across the control groups of the 3 included studies
	71 per 1000	71 per 1000 (57 to 88)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect.

[1]Includes trial(s) at high risk of publication bias.
[2]Unexplained heterogeneity between studies.
[3]Data derived from a single study with uncertainty about the effect size due to poor precision.
[4]Includes trial(s) at high risk of attrition bias.

BACKGROUND

Description of the condition

Acute otitis media (AOM) is one of the most common infectious diseases in children. Eighty per cent of children in high-income countries experienced at least one episode of AOM by the age of three years (Vergison 2010). With the advent of the pneumococcal conjugate vaccine (PCV), two clinical trials showed a reduction of 7%, Fireman 2003, and 6%, Eskola 2001, in otitis media rates. The rate of ambulatory visits for otitis media also declined by between 6% and 20% in children aged less than two years after the introduction of PCV in the United States vaccination programme, with no significant decrease in outpatient visit rates for pneumonia or other acute respiratory infections (Grijalva 2006; Marom 2014; Poehling 2004).

'Otitis media' is a broad term for any middle ear infection or inflammation. It can present as (i) otitis media with effusion (OME): fluid behind an intact tympanic membrane without the symptoms or signs of AOM; (ii) AOM: fluid behind the tympanic membrane with the symptoms or signs of an acute infection; or (iii) chronic suppurative otitis media (CSOM): persistent discharge of pus through a perforated tympanic membrane for more than six weeks (Leach 2011). Several risk factors for AOM have been identified, such as siblings with otitis media, bottle-feeding, attending day-care centres, allergies to environmental entities, belonging to a low socioeconomic group, exposure to tobacco smoke, and family history of otitis media (Erdivanli 2012; Siddartha 2012).

In the past, AOM was generally considered to be viral, but with optimal bacteriological techniques and a good diagnosis it has been shown that over 87% of AOM cases are bacterial in origin (Block 1995; Heikkinen 2003), but commonly triggered by a viral infection. In a 14-year cohort study among children attending day care, viral pathogens, especially respiratory syncytial virus, influenza virus, and adenovirus, conferred a greater risk of developing AOM (Henderson 1982; Jacobs 1998). Respiratory viruses were isolated in 42% of middle ear fluid specimens from children with AOM (Monobe 2003), and influenza viruses accounted for up to 28.4% of viral detections (Yano 2009).

A Cochrane Review showed that antibiotics reduced tympanic membrane perforations and contralateral AOM episodes. However, adverse events such as vomiting, diarrhoea, and rash were more common in children who received antibiotics (Venekamp 2015). A separate Cochrane Review showed that administration of short-course antibiotics (less than seven days) increased the likelihood of relapse and recurrence (Kozyrskyj 2010). The findings of these reviews have led to guidelines recommending limiting or delaying the use of antibiotics, and a policy of 'watchful waiting' has been recommended for some children (Lieberthal 2013). Antibiotics given for six weeks or longer reduced the risk of future episodes of AOM by 50%, with no significant reported side effects such as allergic reactions and diarrhoea (Leach 2011). Antibiotics for OME given continuously for four weeks and three months have shown beneficial effects (Venekamp 2016). However, the issue of antibiotic resistance needs to be considered.

Acute otitis media is clinically diagnosed based on a history of acute onset, signs and symptoms of middle ear inflammation, and presence of middle ear effusion with either a bulging tympanic membrane, decreased mobility, or an air-fluid level. Determination of some of the criteria may necessitate the use of pneumatic otoscopy to demonstrate a decrease in tympanic membrane mobility (Lieberthal 2004).

Description of the intervention

There are two types of influenza vaccine: trivalent inactivated influenza vaccine (TIV) and live attenuated influenza vaccine (LAIV). Trivalent inactivated influenza vaccine is approved for children as young as six months, and LAIV, which is based on cold-adapted, temperature-sensitive vaccine viruses, is approved for children aged two years or older. Annual influenza vaccination is recommended for all children aged six months to eight years. If the children have not been previously vaccinated, two doses four weeks apart are recommended. If the child was vaccinated the previous year, the child will receive only one vaccine dose. However, the recommendations regarding the number of doses might change if vaccine antigens change (CDC 2011).

Cochrane Reviews reported that in preventing influenza among children aged more than two years, live influenza vaccines showed a higher efficacy than inactivated influenza vaccines (82% versus 59%), while in preventing influenza-like illness, the effectiveness was similar (33% versus 36%). Little evidence is available for children younger than two years (Jefferson 2012). A modest effect of the vaccine on influenza was reported in the general population (Jefferson 2014).

A report by the Institute of Medicine looking at 27 adverse events showed that only one study supported a causal relationship between influenza vaccine and anaphylaxis; one study supported a causal relationship for oculo-respiratory syndrome; and two studies supported rejection of a causal relationship for Bell's palsy and asthma exacerbation or reactive airway disease episodes. The evidence for the remaining 23 adverse events (85%) was insufficient to support or reject a causal link due to weak or absent methodology (Stratton 2011).

How the intervention might work

A Cochrane Review revealed that pneumococcal vaccine had marginally beneficial effects for preventing AOM (Fortanier 2014). However, since AOM is often preceded by a viral infection, it is possible that influenza vaccines might be effective in preventing the development of AOM.

Why it is important to do this review

The Advisory Committee on Immunization Practices (ACIP) has recommended influenza vaccination for all children aged six months or older in the USA (CDC 2011). There are many factors that influence parents' decisions whether or not to vaccinate their child (Bhatt 2011). Information on the effect of influenza vaccine on AOM might help parents in this decision. The aim of this review was therefore to report the effect of influenza vaccine on the occurrence of AOM in infants and children.

OBJECTIVES

To assess the effectiveness of influenza vaccine in reducing the occurrence of acute otitis media (AOM) in infants and children.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials comparing influenza vaccine with placebo or no treatment. We included blinded and open-label studies.

Types of participants

Infants and children aged younger than six years old of either sex and of any ethnicity, with or without a history of recurrent AOM.

Types of interventions

Vaccination with any influenza vaccine, live or inactivated, and whole, split-virus, or subunit-type vaccines. Vaccines may be monovalent or polyvalent, single dose or multidose, and administered by any route of administration.

Comparison: placebo or no treatment.

Types of outcome measures

Acute otitis media must be clinician diagnosed. We excluded studies in which diagnosis of AOM was based on the child or carer report alone. The follow-up period for primary outcomes was at least six months after vaccination.

Primary outcomes

1. Number of children having at least one episode of AOM during the follow-up period.
2. Number of episodes of AOM recorded during the follow-up period.

Secondary outcomes

1. Use of antibiotics to treat AOM and its complications.
2. Causative organism associated with AOM.
3. Utilisation of healthcare and related resources.
4. Number of culture-confirmed influenza cases.
5. Adverse events (e.g. febrile illness).

Search methods for identification of studies

Electronic searches

We searched:

- the Cochrane Central Register of Controlled Trials, which includes the Cochrane Acute Respiratory Infections Group's Specialised Register (CENTRAL; 2017, Issue 1) in the Cochrane Library (searched 15 February 2017);
- MEDLINE Ovid (1946 to 15 February 2017);
- Embase.com (1947 to 15 February 2017);
- CINAHL (Cumulative Index to Nursing and Allied Health Literature) (1981 to 15 February 2017);
- LILACS (Latin American and Caribbean Health Sciences Literature) (1982 to 15 February 2017);
- Web of Science (1955 to 15 February 2017).

We used the search strategy in Appendix 1 to search MEDLINE and CENTRAL. We combined the MEDLINE search strategy with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximising version (2008 revision); Ovid format (Lefebvre 2011). We adapted the search strategy for Embase (Appendix 2), CINAHL (Appendix 3), LILACS (Appendix 4), and Web of Science (Appendix 5). We did not impose any language or publication restrictions.

We searched for completed and ongoing trials in two trial registries:

- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/en/; searched 15 February 2017).
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov; searched 15 February 2017).

Searching other resources

We checked the reference lists of all related studies for further references in order to find unpublished trials or trials not identified by the electronic searches. We contacted pharmaceutical companies that market influenza vaccine to identify other related unpublished trials and ongoing trials.

Data collection and analysis

Selection of studies

Two review authors (MNN, MYA) independently scanned the titles and abstracts identified by the searches, obtaining the full-text articles for records that appeared to meet the eligibility criteria or for which information was insufficient to assess eligibility. We independently assessed the eligibility of the trials and documented the reasons for exclusion. Any disagreements were resolved between the review authors by discussion. We contacted the trial authors for clarification where required. We translated papers in languages other than English with the help of the Cochrane Acute Respiratory Infections Group.

Data extraction and management

We extracted the following from each of the selected studies:

- study setting;
- participant characteristics (age, sex, ethnicity);
- methodology (number of participants randomised and analysed, duration of follow-up);
- type of vaccine used;
- method for diagnosing AOM;
- occurrence of AOM and middle ear effusion;
- antibiotics used to treat AOM and its complications;
- causative organism associated with AOM;
- utilisation of healthcare and related resources;
- number of culture-confirmed influenza cases; and
- occurrence of adverse events related to influenza vaccine (e.g. febrile illnesses).

We resolved any disagreements by discussion.

Assessment of risk of bias in included studies

We assessed the risk of bias based on random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, completeness of outcome data,

selectivity of outcome reporting, and other bias, as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Measures of treatment effect

We measured the trials with categorical outcomes using risk ratios (RR) and 95% confidence intervals (CI) and calculated risk differences (RD) and 95% CI. We calculated the number needed to treat for an additional beneficial outcome (NNTB) along with a 95% CI for the first primary outcome. Had we encountered numerical outcomes, we intended to analyse these using mean differences (MD) and 95% CI.

Unit of analysis issues

We checked included trials for unit of analysis errors and did not encounter any. Had we encountered any cluster-randomised controlled trials, we intended to adjust the results from trials showing unit of analysis errors based on the mean cluster size and intracluster correlation coefficient (Higgins 2011).

Dealing with missing data

We contacted the original trial authors to request missing or inadequately reported data (Bergen 2004; Kosalaraksa 2015). We performed analyses on the available data in the event that missing data were not available.

Assessment of heterogeneity

We assessed the presence of heterogeneity in two steps. First, we assessed obvious heterogeneity at face value by comparing populations, settings, interventions, and outcomes. Second, we assessed statistical heterogeneity by means of the I^2 statistic (Higgins 2011).

Assessment of reporting biases

If there were sufficient studies, we intended to use funnel plots to assess the possibility of reporting biases or small-study biases, or both.

Data synthesis

We examined heterogeneity using both fixed-effect and random-effects models, depending on the degree of significant clinical or statistical heterogeneity, in Review Manager 5 software (RevMan 2014). Our results are reported with the fixed-effect model unless it is stated that we have used the random-effects model. Thresholds for the interpretation of the I^2 statistic can be misleading, since the importance of inconsistency depends on several factors. We used the guide to interpret heterogeneity as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011): 0% to 40% might not be important; 30% to 60% may represent moderate heterogeneity; 50% to 90% may represent substantial heterogeneity; and 75% to 100% would be considerable heterogeneity.

GRADE and 'Summary of findings' table

We created a 'Summary of findings' table using the following outcomes: at least one episode of AOM; courses of antibiotics; fever; rhinorrhoea; and pharyngitis.

We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of a body of evidence as it relates to the studies that contribute data to the meta-analyses for the prespecified outcomes (Atkins 2004). We used methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), employing GRADEpro GDT software (GRADEpro 2014). We justified all decisions to down- or upgrade the quality of studies using footnotes, and made comments to aid the reader's understanding of the review where necessary.

Subgroup analysis and investigation of heterogeneity

We planned the following subgroup analyses:

1. age of children, e.g. above and below two years old;
2. first episode and recurrence of AOM;
3. day-care and non-day-care children;
4. type and route of vaccine administration.

We were unable to carry out all of the subgroup analyses in the categories outlined in the protocol due to insufficient data. However, we conducted subgroup analyses on number of children having at least one episode of AOM by course and type of vaccine.

In the original publication of this review we included a subgroup analysis on number of children having at least one episode of AOM by setting and season. We also included subgroup analysis by utilisation of health care, that is hospital admission and patient visits to primary care and the emergency department, because this might differ between different healthcare settings. For example, in some settings, users might be more likely to be hospitalised for relatively minor adverse effects. We specified the subgroup analyses in order to explore this as a possible reason for heterogeneity.

We did not perform a subgroup analysis by type of adverse event, but have reported each type of adverse event in the included studies as a separate analysis.

We explored the potential sources of heterogeneity. When important heterogeneity was present, we use a random-effects model (DerSimonian 1986).

Sensitivity analysis

We performed a sensitivity analysis to investigate the impact of risk of bias for sequence generation and allocation concealment of included studies.

RESULTS

Description of studies

See: Characteristics of included studies, Characteristics of excluded studies, and Characteristics of studies awaiting classification tables.

Results of the search

In the original publication of this review, we retrieved 319 records from the search of the electronic databases and 12 records from other sources (Figure 1). We screened a total of 331 records. We reviewed full copies of 28 studies, of which 14 articles possibly met the review inclusion criteria and 14 were not eligible for inclusion. Three of those not eligible for inclusion were systematic reviews

and meta-analyses that were related to our research question (Block 2011; Heikkinen 2013; Prutsky 2014). We categorised one trial as awaiting classification, as it included children aged one to eight years (Bergen 2004); we contacted the trial authors for further information on the age group of study participants. Two trials were not eligible as they were quasi-randomised (Cuhaci 2012; Heikkinen 1991). We therefore included 10 trials and excluded 12 trials from the initial review, while one trial awaited classification.

Figure 1. Study flow diagram.

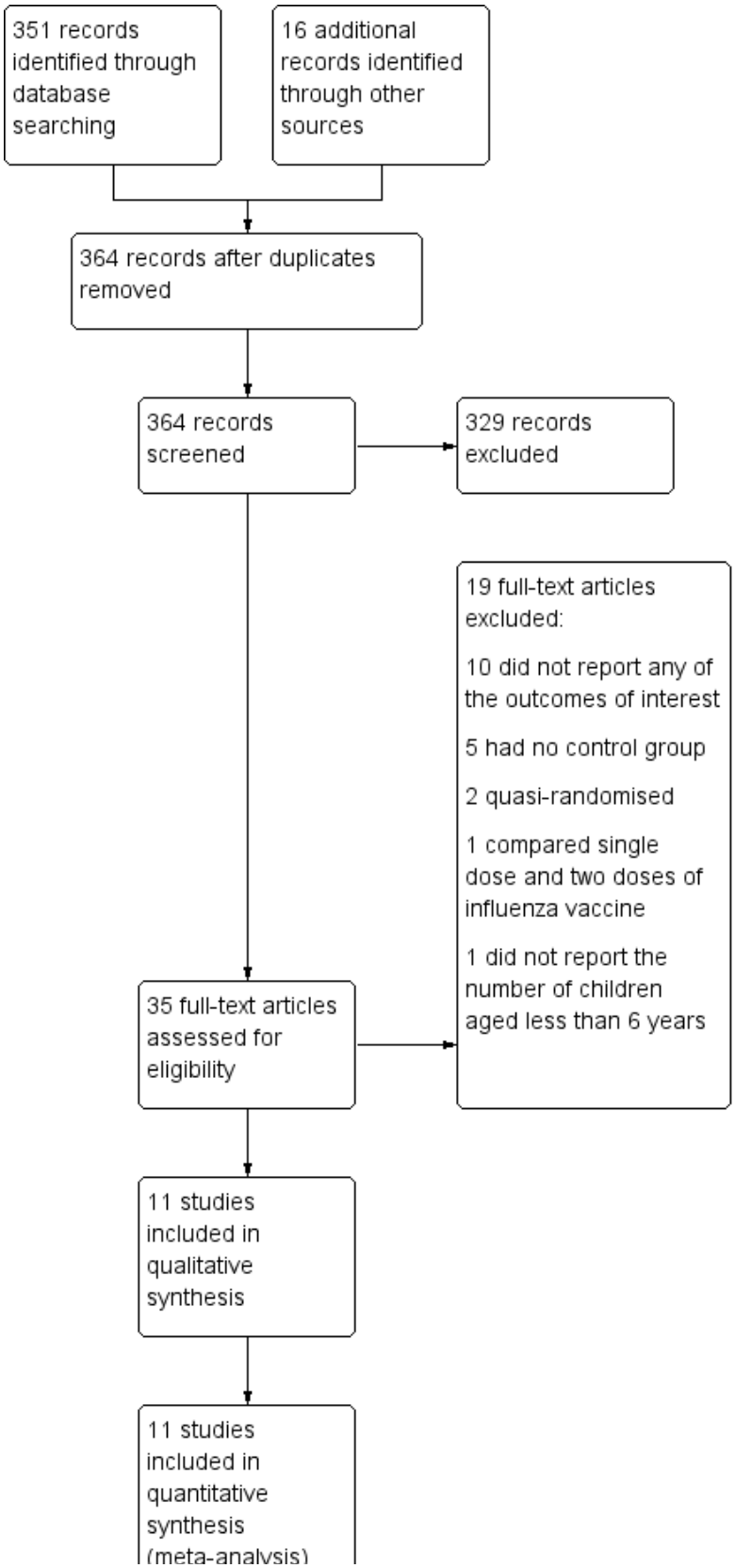
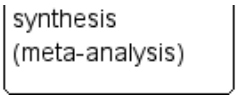


Figure 1. (Continued)



In this 2017 update, we excluded a study previously awaiting classification because it included children aged one to eight years, and we were not able to ascertain the number or proportion of children below six years of age (Bergen 2004). We retrieved 32 additional records from the search of the electronic databases and four records from other sources. We screened a total of 33 records. We reviewed the full texts of seven studies, identifying one trial as meeting the review inclusion criteria (Kosalaraksa 2015), and six as not eligible for inclusion. We have therefore included a total of 11 trials and excluded 19 trials in this review update.

Included studies

We included 10 trials (N = 16,707) in the initial review (Belshe 2000; Bracco 2009; Clements 1995; Gruber 1996; Hoberman 2003; Lum 2010; Marchisio 2002; Swierkosz 1994; Tam 2007; Vesikari 2006), and added one further trial (N = 416) in this update (Kosalaraksa 2015), resulting in a total of 11 included studies involving 17,123 children. Ten out of the 11 included studies (and all five that contributed to the primary outcome) declared funding from vaccine manufacturers (Belshe 2000; Bracco 2009; Clements 1995; Gruber 1996; Hoberman 2003; Kosalaraksa 2015; Lum 2010; Marchisio 2002; Tam 2007; Vesikari 2006).

Participants

Six of the 11 trials were conducted in high-income countries (Clements 1995; Gruber 1996; Hoberman 2003; Marchisio 2002; Swierkosz 1994; Vesikari 2006) and five were multicentre trials in high-, middle-, and low-income countries (Belshe 2000; Bracco 2009; Kosalaraksa 2015; Lum 2010; Tam 2007). Eight of the 11 trials recruited participants from healthcare settings (Belshe 2000; Bracco 2009; Gruber 1996; Hoberman 2003; Lum 2010; Marchisio 2002; Tam 2007; Vesikari 2006), and one trial recruited participants from day-care centres (Clements 1995). Two trials did not mention the setting from which the participants were recruited (Kosalaraksa 2015; Swierkosz 1994). Nine trials reported exclusion of participants due to an acute illness, immunosuppression or receiving medications known to suppress the immune system, or with craniofacial abnormality (Belshe 2000; Bracco 2009; Clements 1995; Hoberman 2003; Kosalaraksa 2015; Lum 2010; Marchisio 2002; Tam 2007; Vesikari 2006). Seven trials involving 8154 children mentioned the sex of the children, and these were equally distributed throughout the seven trials and across the intervention and comparison groups (Clements 1995; Hoberman 2003; Kosalaraksa 2015; Lum 2010; Marchisio 2002; Tam 2007; Vesikari 2006). For one trial, the denominator (number of children who had the outcome measured) was unclear, so we used the number randomised as the denominator based on the intention-to-treat principle (Clements 1995).

Intervention

Participants in the trials were randomised into intervention and control groups. The intervention was a trivalent vaccine in six trials (Belshe 2000; Clements 1995; Hoberman 2003; Swierkosz 1994; Tam 2007; Vesikari 2006), reassortant in two trials (Bracco 2009; Lum 2010), and a combination of monovalent and bivalent in one trial (Gruber 1996). Live attenuated vaccine was administered in seven trials (Belshe 2000; Bracco 2009; Gruber 1996; Lum 2010; Swierkosz 1994; Tam 2007; Vesikari 2006), virosomal subunit in one trial (Marchisio 2002), subvirion in two trials (Clements 1995; Hoberman 2003), and split virion in one trial (Kosalaraksa 2015). The vaccines were administered intranasally in seven trials (Belshe 2000; Bracco 2009; Gruber 1996; Marchisio 2002; Swierkosz 1994; Tam 2007; Vesikari 2006), intramuscularly in two trials (Hoberman 2003; Kosalaraksa 2015), and subcutaneously in one trial (Lum 2010). Five trials gave a single course of one to three doses (Clements 1995; Gruber 1996; Lum 2010; Marchisio 2002; Swierkosz 1994), and six trials gave two courses, where the first course was either one or two doses and the second course was a single dose given six months to one year later (Belshe 2000; Bracco 2009; Hoberman 2003; Kosalaraksa 2015; Tam 2007; Vesikari 2006). For those trials that gave two courses, follow-up was reported for at least six months after each course was completed.

Outcomes

Eight trials reported measuring the number of children with at least one episode of AOM during follow-up (Bracco 2009; Clements 1995; Gruber 1996; Hoberman 2003; Lum 2010; Marchisio 2002; Swierkosz 1994; Vesikari 2006). However, only three trials met our prespecified duration of follow-up of at least six months (Hoberman 2003; Lum 2010; Vesikari 2006). We included one additional trial with a five-month follow-up period in the review (Clements 1995). This trial was conducted in a setting that had a distinct respiratory season, and the children were followed up for the respiratory season, which explained the shorter follow-up. Our primary outcomes were reported. We made a post hoc decision to include this trial despite not quite reaching our inclusion criteria of six months' follow-up, testing this decision in our sensitivity analysis. The remaining trials all had short follow-up periods of eight weeks or less, therefore we excluded the primary outcome data and only reported secondary outcomes from these trials. One trial randomised children into one of four regimens: (i) two doses of LAIV; (ii) single-dose LAIV; (iii) excipient placebo; or (iv) saline placebo with six to 36 months' follow-up (Bracco 2009). However, the numbers of children in group (iii) and (iv) were not reported, therefore we could not include this trial in the meta-analysis. We included four trials in the meta-analysis for the primary outcomes (Clements 1995; Hoberman 2003; Lum 2010; Vesikari 2006). One trial involving 1602 children reported the mean episodes per person without a measure of dispersion that could be used to calculate the standard deviation, hence we were unable to analyse this outcome (Belshe 2000). For those trials that gave two courses of vaccine, we reported the first primary outcome for the follow-up period after the first course (Belshe 2000; Hoberman 2003; Vesikari 2006), which we felt allowed for better consistency across the included trials. However, we have also included a subgroup analysis of the first primary outcome by number of courses.

Ten trials reported our secondary outcomes (Belshe 2000; Bracco 2009; Gruber 1996; Hoberman 2003; Kosalaraksa 2015; Lum 2010; Marchisio 2002; Swierkosz 1994; Tam 2007; Vesikari 2006). One trial randomised children in a 3:2 ratio to receive two doses of vaccine

or placebo in year one, and re-randomised children in year two in a 1:1 ratio to receive a single dose of vaccine or placebo without consideration of their group assignment in the first year (Tam 2007). The findings were therefore obtained cumulatively from both years.

Excluded studies

We excluded 19 trials. Ten trials did not report any of our outcomes of interest (Belshe 1998; Belshe 2007; Esposito 2003; Forrest 2008; Gruber 1997; Longini 2000; Maeda 2004; Principi 2003; Thors 2016; Vesikari 2011). Three trials compared different types of influenza vaccine (Brady 2014; Langley 2015; Loeb 2016), and five trials had no control group (Ashkenazi 2006; Brady 2014; Houdouin 2016; Langley 2015; Loeb 2016). Two trials applied quasi-randomisation (Cuhaci 2012; Heikkinen 1991), and one trial compared a single dose with two doses of influenza vaccine (Han 2015). We excluded one trial because the data for the number or proportion of children aged less than six years were not available (Bergen 2004). The details of these trials are provided in the Characteristics of excluded studies table.

Risk of bias in included studies

The assessment of risk of bias is shown in Figure 2 and Figure 3. Figure 2 shows the proportion of studies assessed as low, high, or unclear risk of bias for each 'Risk of bias' indicator. Figure 3 shows the 'Risk of bias' indicators for individual studies. See the Characteristics of included studies table.

Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

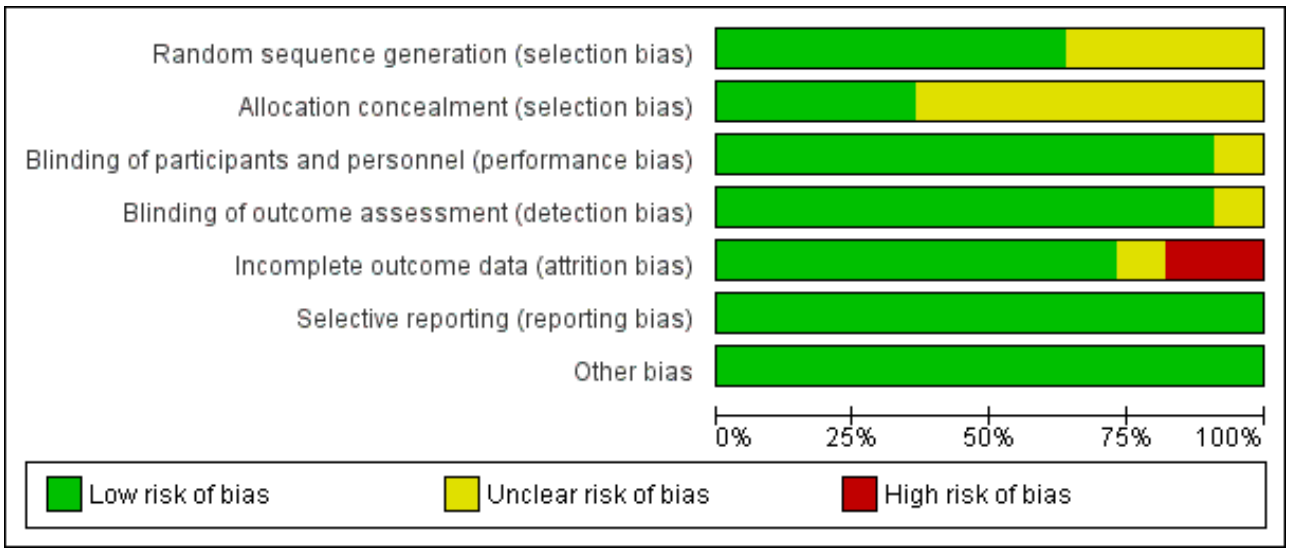
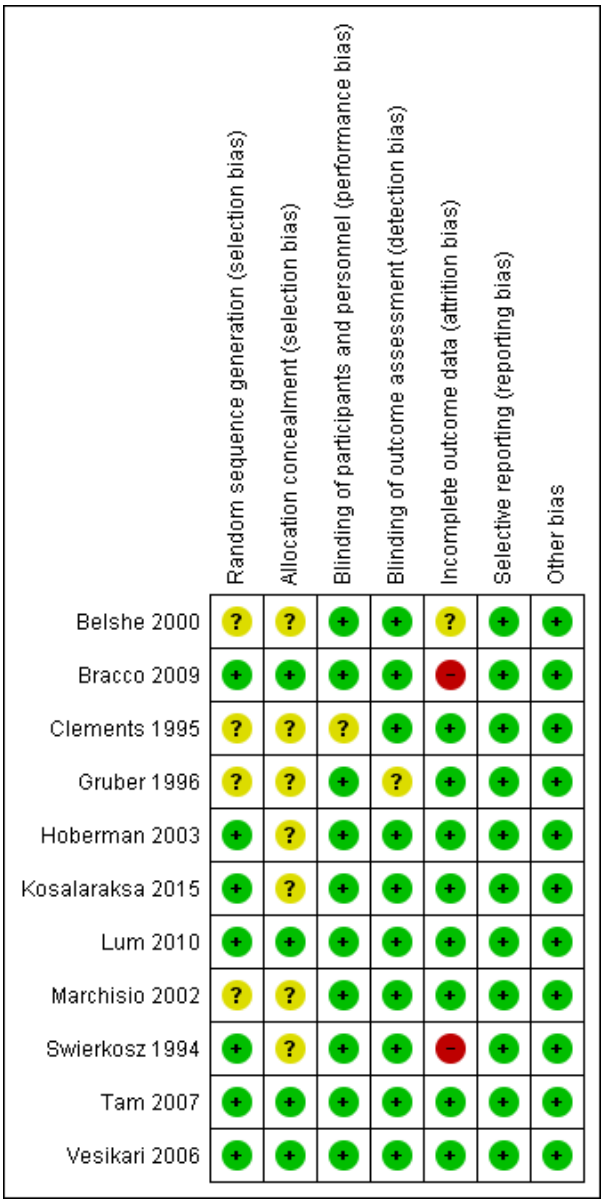


Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Seven trials (including one trial of 2821 children not in the meta-analysis, Bracco 2009) described the method of randomisation used. Two trials randomised the children according to a preprinted allocation list (Bracco 2009; Vesikari 2006); three trials used computer-generated randomisation (Hoberman 2003; Lum 2010; Tam 2007); and one trial used an internet-based system (Kosalaraksa 2015). Swierkosz 1994 applied a simple randomisation with a ratio of one placebo to every two or three children who received the intervention. The remaining four trials did not report the method of randomisation, thus we assessed random sequence generation as unclear risk of bias (Belshe 2000; Clements 1995; Gruber 1996; Marchisio 2002). We assessed allocation concealment as unclear in seven trials (Belshe 2000; Clements 1995; Gruber 1996; Hoberman 2003; Kosalaraksa 2015; Marchisio 2002; Swierkosz 1994).

Blinding

Nine trials used a placebo control (Belshe 2000; Bracco 2009; Gruber 1996; Hoberman 2003; Kosalaraksa 2015; Lum 2010; Swierkosz 1994; Tam 2007; Vesikari 2006), and one trial gave no treatment to the control group (Marchisio 2002). In the latter trial, the parents were asked not to inform the outcome assessors of the group assignment, and only the investigators were blinded to group assignment (Marchisio 2002). The control group in one trial received hepatitis B immunisation, and blinding was not described in this trial (Clements 1995).

Incomplete outcome data

Five trials measured the primary outcomes and were included in the meta-analysis. Of these, three trials administered two courses of vaccine, that is at year one (one or two doses) and year two (single dose) (Belshe 2000; Hoberman 2003; Vesikari 2006), and

two trials administered one course of vaccine (one or two doses) (Clements 1995; Lum 2010). Five trials measured the primary outcome at six to eight months (Belshe 2000; Clements 1995; Hoberman 2003; Lum 2010; Vesikari 2006), and one trial measured outcomes at one year (Hoberman 2003). All five trials had less than 20% loss to follow-up.

We did not include Bracco 2009 in the meta-analysis for the first primary outcome as the follow-up period was too short. Due to the treatment allocation coding and a labelling error in the second season, 683 of 2054 children were excluded because they received a treatment other than that to which they were randomised. Thus, the year two per-protocol response rate was 42.6%. However, data on adverse effects for the second season were supplied by the trial authors and could be included in the meta-analysis of adverse effects. Ten trials measured secondary outcomes, and in all of these the non-response rate was less than 10% (Belshe 2000; Bracco 2009; Gruber 1996; Hoberman 2003; Kosalaraksa 2015; Lum 2010; Marchisio 2002; Swierkosz 1994; Tam 2007; Vesikari 2006).

Eight trials performed an intention-to-treat analysis in which the children were analysed according to the groups to which they were initially assigned (Belshe 2000; Bracco 2009; Clements 1995; Hoberman 2003; Lum 2010; Marchisio 2002; Tam 2007; Vesikari 2006). In Gruber 1996, 182 children were assigned into vaccine and control groups. However, the analysis of two vaccinated children was not included. In Swierkosz 1994, the analyses were based on 22, 18, and 14 children for day 0, day 60, and day 120, respectively.

Selective reporting

All 11 trials reported the outcomes as specified in their methods section (Belshe 2000; Bracco 2009; Clements 1995; Gruber 1996; Hoberman 2003; Kosalaraksa 2015; Lum 2010; Marchisio 2002; Swierkosz 1994; Tam 2007; Vesikari 2006).

Only two trials were prospectively registered in the WHO ICTRP and ClinicalTrials.gov (Kosalaraksa 2015; Lum 2010). The outcomes listed in the registered protocols were the same as those reported. We had no access to protocols for nine trials, but all the expected outcomes were reported (Belshe 2000; Clements 1995; Gruber 1996; Hoberman 2003; Lum 2010; Marchisio 2002; Swierkosz 1994; Tam 2007; Vesikari 2006).

Other potential sources of bias

We detected no other potential sources of bias.

Effects of interventions

See: **Summary of findings for the main comparison** Influenza vaccine compared to control for preventing acute otitis media in infants and children

Primary outcomes

1. Number of children having at least one episode of acute otitis media during the follow-up period

Our prespecified outcome was number of children having at least one episode of AOM. Four trials reported at least one episode of AOM during a follow-up period of at least six months after one course of vaccine (Clements 1995; Hoberman 2003; Lum 2010; Vesikari 2006) (Analysis 1.1; risk ratio (RR) 0.84, 95% confidence interval (CI) 0.69 to 1.02; risk difference (RD) -0.04, 95% CI -0.08 to 0.00 random-effects; I^2 = 56%, number needed to treat for an additional beneficial outcome (NNTB) 25, 95% CI 12.5 to 100; 4 trials; 3134 children; low-quality evidence).

Acute otitis media by courses of vaccine

Four trials reported at least one episode of AOM during a follow-up period of at least six months after the first course of vaccine, and these were included in our primary analysis as above (Analysis 1.1) (Clements 1995; Hoberman 2003; Lum 2010; Vesikari 2006). There was no difference in this outcome by the number of doses (one or two doses in the first course) of vaccine. For those trials that included two courses of vaccine, two trials involving 1447 children showed no difference between the influenza vaccine and control group in AOM during the follow-up period after the second course (Analysis 1.2) (Hoberman 2003; Vesikari 2006).

Acute otitis media by trial setting

Recruitment for three trials took place in the healthcare setting (Hoberman 2003; Lum 2010; Vesikari 2006), and for one trial in a day-care setting (Clements 1995). Due to the small number of studies in this subgroup, we did not do a subgroup analysis by trial setting for this update of the review.

Acute otitis media by season

Two trials documented this outcome according to season, either the respiratory or the influenza season. The vaccine was administered at the beginning of the season in two trials (Clements 1995; Hoberman 2003). One trial reported AOM during the respiratory season (Hoberman 2003). We did not perform a subgroup analysis due to the limited number of studies reporting season.

Acute otitis media by type of vaccine

Of the four studies that reported the outcome of at least one episode of AOM during the follow-up period, only two types of vaccine were used, trivalent cold-adapted vaccine, in Lum 2010 and Vesikari 2006, and trivalent subvirion vaccines, in Clements 1995 and Hoberman 2003. There was substantial heterogeneity in the two subgroups and in the overall result. The two subgroups failed to show a difference in AOM, and there was no significant difference between the subgroups (Analysis 1.3).

2. Number of episodes of acute otitis media recorded during the follow-up period

One trial involving 396 children reported this outcome but without a measure of variance, hence we were unable to analyse this outcome (Hoberman 2003).

Secondary outcomes

1. Use of antibiotics to treat acute otitis media and its complications

Two trials reported the number of children who received any antibiotics over the follow-up period (Marchisio 2002; Vesikari 2006). Marchisio 2002 (N = 133) reported antibiotics prescribed for AOM, and Vesikari 2006 (N = 1090) reported antibiotics prescribed for influenza-like illness including AOM (Analysis 1.4; 2 trials; 1223 children; RR 0.70, 95% CI 0.59 to 0.83; RD -0.11, 95% CI -0.16 to -0.06; I^2 = 0%; moderate-quality evidence). One trial reported the mean courses of antibiotics, but as the data appeared to be skewed, we were unable to perform a meta-analysis (Hoberman 2003).

2. Causative organism associated with acute otitis media

None of the studies reported on this outcome.

3. Utilisation of healthcare and related resources

Utilisation of healthcare resources refers to any reported self referral by a trial participant to a healthcare provider during the follow-up period. One trial reported the number of children who were hospitalised during the follow-up period (Hoberman 2003). This trial showed no difference between the influenza vaccine and control groups in rate of hospitalisation. One trial reported the mean visits to primary care, emergency department, or hospital admission, but as the data appeared to be skewed, we were unable to include these data in a meta-analysis (Hoberman 2003).

4. Number of culture-confirmed influenza cases

Three trials reported the number of culture-confirmed influenza cases (Belshe 2000; Lum 2010; Vesikari 2006). In the vaccine group, there was a significant reduction in the number of culture-confirmed influenza cases with considerable heterogeneity (3 trials; 4449 children, random-effects; RR 0.07, 95% CI 0.02 to 0.17; RD -0.02, 95% CI -0.04 to -0.01; I^2 = 84%).

5. Adverse events

Seven trials reported measuring adverse events. There was a significant increase in the number of children with febrile reaction in the vaccine group (Analysis 1.5; 7 trials; 10,615 children; RR 1.15, 95% CI 1.06 to 1.24; RD 0.02, 95% CI 0.00 to 0.04; I^2 = 0%; low-quality evidence) (Bracco 2009; Gruber 1996; Kosalaraksa 2015; Lum 2010; Swierkosz 1994; Tam 2007; Vesikari 2006).

Six trials reported a significant increase in the number of children with rhinorrhoea in the vaccine group (Analysis 1.6; 6 trials; 10,563 children; RR 1.17, 95% CI 1.07 to 1.29; RD 0.09, 95% CI 0.01 to 0.16; I^2 = 63%; low-quality evidence) (Bracco 2009; Gruber 1996; Lum 2010; Swierkosz 1994; Tam 2007; Vesikari 2006).

Three trials reported pharyngitis (Bracco 2009; Lum 2010; Vesikari 2006). There was no difference between the vaccine and control groups (Analysis 1.7).

Additional adverse events were reported in this update. One trial reported the number of children with drowsiness, irritability/fussiness, and loss of appetite (Kosalaraksa 2015). This trial showed a significant difference between influenza vaccine and control groups in rate of drowsiness (1 trial; 416 children; RR 1.45, 95% CI 1.01 to 2.06; RD 0.11, 95% CI 0.01 to 0.20; P = 0.04). This trial showed no difference in rates of irritability/fussiness (1 trial; 416 children; RR 1.33, 95% CI 1.00 to 1.77; RD 1.11, 95% CI 0.01 to 0.21) and loss of appetite (1 trial; 416 children; RR 1.13, 95% CI 0.78 to 1.64; RD 0.03, 95% CI -0.06 to 0.12) between the influenza vaccine and control groups.

Sensitivity analysis

For all outcomes, there was no substantial change in the effect sizes and CI after removing the trials with unclear risk of bias for allocation concealment and random sequence generation. The inclusion of a trial with a five-month follow-up period (Clements 1995), shorter than our predefined follow-up of at least six months, did not substantially affect our results.

DISCUSSION

Summary of main results

This review was designed to include all randomised controlled trials (RCTs) addressing the effectiveness of influenza vaccine in reducing the occurrence of acute otitis media (AOM) in infants and children. The 11 identified trials formed a heterogeneous group addressing several comparisons and a variety of outcomes, resulting in few trials contributing to each of our predefined outcomes.

There was a 4% absolute reduction in episodes of AOM among vaccinated children during the follow-up period. The subgroup analyses (i.e. number of courses or types of vaccine administered) showed no difference. There was a clinically important 11% absolute reduction in children receiving an antibiotic for AOM or its complications. We were unable to demonstrate whether there was any difference in utilisation of health care between the vaccine and control groups for the one included trial. Reporting of adverse events was limited to minor side effects, which included episodes of fever, rhinorrhoea, and drowsiness, and these were increased with the vaccine. We were unable to pool the results for all adverse events because some children may have experienced more than one adverse event.

Overall completeness and applicability of evidence

We performed a comprehensive and extensive literature review to assess the effectiveness of influenza vaccine in reducing the occurrence of AOM in infants and children. We included 11 trials, but the findings of this review may not be applicable to children aged less than six months or more than six years, as they were excluded from the included trials. Nevertheless, the age ranges in the included studies do represent the age range of children at risk of AOM (MeReC 2006). We could not include five of the 11 trials in the meta-analysis because the follow-up period was too short. One trial was not included due to a very high rate of attrition, and 13,989 children were not included in the primary outcome. This limits the applicability of the findings of this review. None of the 11 included trials examined the causative organism associated with AOM. Our review evaluated monovalent, bivalent, or trivalent influenza vaccine as single, two, or three doses given between seven to 60 days apart, but was not able to show whether the number of doses made a difference in the occurrence of AOM. Although the immunogenicity of the vaccine for one, two, and three doses has been studied (Swierkosz 1994), we are unaware of any direct comparisons of different doses that looked at clinically important outcomes. From the reported incidence of adverse events, we were able to detect common side effects, that is febrile reactions to vaccination, rhinorrhoea, pharyngitis, and drowsiness. The information on adverse events came from seven trials involving about 10,000 children, but there was a lack of information on more rare and serious adverse events. However, in a Cochrane Review examining the efficacy and safety of influenza vaccine in healthy children, there were reports of additional rare or serious adverse events over and above those reported in the trials included in our review (Jefferson 2012). These included lower respiratory infections, septicaemia, and death. However, none of the trial investigators judged these rare events to be due to the vaccine.

Quality of the evidence

Overall, we judged the quality of evidence to be low to moderate, but judged evidence for adverse events to be of low quality. Generally, there was a low or unclear risk of bias for most trials in most domains. There was no access to protocols in nine trials. However, we judged selective reporting bias to be low because all the expected outcomes had been reported. Only two trials were prospectively registered on a trial registration database. Four studies had unclear risk of bias for method of randomisation and allocation concealment, of which two, described as double-blind, placebo-controlled studies, contributed to the first primary outcome. Removing these studies on sensitivity analysis did not substantially change the effect estimate or the confidence, so we have not downgraded for this.

Risk of attrition bias was present in two trials. Both of these studies only contributed to the adverse effects outcomes, therefore we have downgraded these outcomes for risk of bias. Attrition bias was unclear in one trial due to unexplained reasons for loss to follow-up (Figure 3). Loss to follow-up was less than 20% in six trials, and nine trials carried out intention-to-treat analysis. Ten trials declared funding from vaccine manufacturers, and there is a potential for financial competing interest. We have therefore downgraded all outcomes over concerns about potential publication bias. For most of our meta-analyses, we encountered little or moderate heterogeneity. We have shown the results of the random-effects meta-analysis where there was moderate heterogeneity. Where we have done random-effects meta-analysis, there was no shift in the effect estimate, and although the 95% confidence interval was wider in all instances, the outcome remained significant. Some outcomes showed substantial heterogeneity; where this occurred we have indicated this and not shown the pooled estimate. We downgraded our first primary outcome due to concerns about this. For all studies contributing to this outcome, the effect estimate favoured influenza vaccine, but heterogeneity (I^2 = 62%) reduces our certainty about the size of reduction for this outcome. Using the GRADE approach, we therefore assessed the overall level of evidence contributing to this review as low to moderate quality (Summary of findings for the main comparison).

There was a wide variation among the included studies in the frequency of adverse events reported, suggesting differences in definitions used and difficulty in identifying and reporting adverse events. We have therefore downgraded these adverse events for heterogeneity.

Potential biases in the review process

We attempted to reduce publication bias by checking the reference lists of all related studies for further references and searching multiple databases without language restriction. However, we cannot be certain that we have located all the trials in this area. Although there were 11 included trials, we were not able to construct a funnel plot for detecting bias or heterogeneity due to insufficient studies contributing to each outcome. Not all included trials reported all outcomes. One included trial did not meet our inclusion criteria in terms of the duration of follow-up (Clements 1995). This trial had a maximum follow-up period of five months. This was also the only trial carried out in day-care centres. However, there was no significant difference between this trial and the four trials that recruited children from healthcare settings, although the study with a five-month follow-up period actually reported a higher incidence of AOM. In spite of the fact that the included studies all showed the same direction of effect, we encountered moderate heterogeneity in our first primary outcome. We were unable to demonstrate whether the heterogeneity could be explained by subgroup analysis. However, there were differences in the measurement of AOM. Diagnosis of AOM is subjective, and although attempts were made in all the included studies to make this more objective, the definitions used varied across the studies. Since only two of the included studies were prospectively registered, we cannot be certain that we missed studies that measured AOM but did not report it.

A possible bias in this review is that we excluded one study due to uncertainty of the age of the participants (Bergen 2004). However, the results of this study were consistent with the findings of our review, reporting a significant reduction in otitis media in children one to eight years of age, but reported lower febrile illness in the vaccine group.

Agreements and disagreements with other studies or reviews

Three other systematic reviews have examined the effect of influenza vaccine on otitis media (Block 2011; Heikkinen 2013; Prutsky 2014). Block 2011 evaluated the efficacy of live attenuated influenza vaccine (LAIV), trivalent inactivated influenza vaccine (TIV), and placebo for influenza-associated AOM from RCTs. This review included six placebo-controlled trials and two TIV-controlled trials. Five of the eight trials were included in this review, and the others were excluded for absence of relevant primary or secondary outcomes and the absence of a control group (Belshe 2000; Bracco 2009; Lum 2010; Tam 2007; Vesikari 2006).

Heikkinen 2013 included the same trials as in Block 2011. Prutsky 2014 included seven RCTs and two observational studies. Four of the seven RCTs were included in our review, and the remaining three trials were not related to our prespecified primary or secondary outcomes (Gruber 1996; Lum 2010; Swierkosz 1994; Vesikari 2006).

All three reviews found a reduction in the development of AOM with influenza vaccines, similar to our review. Six of the nine studies in the Prutsky 2014 review showed an increased risk of developing fever in the vaccine group compared to the placebo group, similar to our findings. We found no other systematic reviews that reported our other prespecified secondary outcomes.

The review by Jefferson 2012 on vaccines for preventing influenza in healthy children showed that for live attenuated vaccines, there was an 80% overall reduction in influenza (RR 0.20, 95% CI 0.13 to 0.32). The RR for children under the age of six years old was 0.18 (95% CI 0.11 to 0.29), but little evidence was available for children under two years old.

We consider this to be consistent with other data. In a Cochrane Review on pneumococcal conjugate vaccines (PCV), the 7-valent PCV with CRM197 as carrier protein (CRM197-PCV7) administered during early infancy was associated with a relative risk reduction of all-cause AOM of -5% in high-risk children (95% CI -25% to 12%). Administering PCV7 in healthy infants with a low baseline risk of AOM showed modest beneficial effects, with relative risk reduction of 7% (95% CI 4% to 9%) in three trials (Fortanier 2014). Pneumococcal vaccine had a small effect on AOM in healthy

infants. However, since AOM is preceded by viral infection, a greater reduction in AOM following influenza vaccine is feasible, and the size of the effect we found is consistent with the overall efficacy of the vaccine. Consequently, a reduction in otitis media (RR 0.80) (from 264 to 211 per 1000, i.e. 53 per 1000) (or 5.3%) is compatible with this.

AUTHORS' CONCLUSIONS

Implications for practice

Influenza vaccine appears to have a small beneficial effect in reducing acute otitis media (AOM), resulting in a 4% absolute reduction in children who experienced at least one episode of otitis media. Promoting influenza vaccination solely to reduce AOM therefore does not seem justified, but it may be useful to parents when making a decision whether or not to vaccinate their children. Influenza vaccine appears to be effective in reducing antibiotic usage, and its usage for this purpose might be justified. However, in settings with a low incidence of mastoiditis, where 'watchful waiting' is practised as a means of reducing antibiotic over usage, the impact of this finding is uncertain. The findings of this review would need to be considered in the context of the efficacy of the vaccine, which is reported in a separate review (Jefferson 2014). Data in this review on rarer and serious adverse effects of the vaccine are limited, and more safety data would be needed to assess more fully whether influenza vaccine would be a useful intervention to reduce antibiotic usage. Reduction in the occurrence of AOM was not observed in trials that recruited children in healthcare facilities.

Implications for research

If further studies examining the use of influenza vaccine in young infants and preschool children are to be conducted, they should include AOM as an outcome and provide detailed safety data. Data on antibiotic usage for AOM and other respiratory infections, incidence of mastoiditis, local prescribing patterns, and existing local guidelines that might confound antibiotic usage should also be collected. If studies are conducted in settings with a definite seasonal occurrence, the follow-up period should include the influenza season and be of sufficient duration to ensure that episodes of AOM and recurrent AOM are captured.

ACKNOWLEDGEMENTS

We wish to acknowledge the authors of a previous protocol, Elspeth Kay, Kwong Ng, Allison Salmon, and Chris Del Mar (Kay 2005). The new authors would like to thank Elizabeth Dooley, Managing Editor of the Cochrane Acute Respiratory Infections (ARI) Group, for the comments and feedback during the preparation of this review. We would also like to thank Justin Clark, Information Specialist of the ARI Group, for his assistance with this review update.

REFERENCES

References to studies included in this review

Belshe 2000 *{published data only}*

Belshe RB, Gruber WC. Prevention of otitis media in children with live attenuated influenza vaccine given intranasally. *Pediatric Infectious Disease Journal* 2000;**19**(Suppl 5):66-71.

Bracco 2009 *{published data only}*

Bracco Neto H, Farhat CK, Tregnaghi MW, Madhi SA, Razmpour A, Palladino G, et al. Efficacy and safety of 1 and 2 doses of live attenuated influenza vaccine in vaccine-naive children. *Pediatric Infectious Disease Journal* 2009;**28**(5):365-71. [PUBMED: 19395948]

Clements 1995 *{published data only}*

Clements DA, Langdon L, Bland C, Walter E. Influenza A vaccine decreases the incidence of otitis media in 6- to 30-month-old children in day care. *Archives of Pediatrics & Adolescent Medicine* 1995;**149**(10):1113-7. [PUBMED: 7550814]

Gruber 1996 *{published data only}*

Gruber WC, Belshe RB, King JC, Treanor JJ, Piedra PA, Wright PF, et al. Evaluation of live attenuated influenza vaccines in children 6-18 months of age: safety, immunogenicity and efficacy. *Journal of Infectious Diseases* 1996;**173**(6):1313-9. [PUBMED: 8648202]

Hoberman 2003 *{published data only}*

Hoberman A, Greenberg DP, Paradise JL, Rockette HE, Lave JR, Kearney DH, et al. Effectiveness of inactivated influenza vaccine in preventing acute otitis media in young children: a randomised controlled trial. *JAMA* 2003;**290**(12):1608-16. [PUBMED: 14506120]

Kosalaraksa 2015 *{published data only}*

Kosalaraksa P, Jeanfreau R, Frenette L, Drame M, Madariaga M, Innis BL, et al. AS03B-adjuvanted H5N1 influenza vaccine in children 6 months through 17 years of age: a phase 2/3 randomized, placebo-controlled, observer-blinded trial. *Journal of Infectious Diseases* 2015;**211**(5):801-10. [PUBMED: 25293368]

Lum 2010 *{published data only}*

Lum LC, Borja-Tabora CF, Breiman RF, Vesikari T, Sablan BP, Chay OM, et al. Influenza vaccine concurrently administered with a combination measles, mumps, and rubella vaccine to young children. *Vaccine* 2010;**28**(6):1566-74. [PUBMED: 20003918]

Marchisio 2002 *{published data only}*

Marchisio P, Cavagna R, Maspes B, Gironi S, Esposito S, Lambertini L, et al. Efficacy of intranasal virosomal influenza vaccine in the prevention of recurrent acute otitis media in children. *Clinical Infectious Diseases* 2002;**35**(2):168-74. [PUBMED: 12087523]

Swierkosz 1994 *{published data only}*

Swierkosz EM, Newman FK, Anderson EL, Nugent SL, Mills GB, Belshe RB. Multidose, live attenuated, cold-recombinant, trivalent influenza vaccine in infants and young children. *Journal of Infectious Diseases* 1994;**169**(5):1121-4. [PUBMED: 8169405]

Tam 2007 *{published data only}*

Tam JS, Capeding MR, Lum LC, Chotpitayasunondh T, Jiang Z, Huang LM, et al. Efficacy and safety of a live attenuated, cold-adapted influenza vaccine, trivalent against culture-confirmed influenza in young children in Asia. *Pediatric Infectious Disease Journal* 2007;**26**(7):619-28. [PUBMED: 17596805]

Vesikari 2006 *{published data only}*

Vesikari T, Fleming DM, Aristegui JF, Vertruyen A, Ashkenazi S, Rappaport R, et al. Safety, efficacy and effectiveness of cold-adapted influenza vaccine-trivalent against community-acquired, culture-confirmed influenza in young children attending day care. *Pediatrics* 2006;**118**(6):2298-312. [PUBMED: 17142512]

References to studies excluded from this review

Ashkenazi 2006 *{published data only}*

Ashkenazi S, Vertruyen A, Aristegui J, Esposito S, McKeith DD, Klemola T, et al. Superior relative efficacy of live attenuated influenza vaccine compared with inactivated influenza vaccine in young children with recurrent respiratory tract infections. *Pediatric Infectious Disease Journal* 2006;**25**(10):870-9. [PUBMED: 17006279]

Belshe 1998 *{published data only}*

Belshe RB, Mendelman PM, Treanor J, King J, Gruber WC, Piedra P, et al. The efficacy of live attenuated, cold-adapted, trivalent, intranasal influenza virus vaccine in children. *New England Journal of Medicine* 1998;**338**(20):1405-12. [PUBMED: 9580647]

Belshe 2007 *{published data only}*

Belshe RB, Edwards KM, Vesikari T, Black SV, Walker RE, Hultquist M, et al. Live attenuated versus inactivated influenza vaccine in infants and young children. *New England Journal of Medicine* 2007;**356**(7):685-96. [PUBMED: 17301299]

Bergen 2004 *{published data only}*

Bergen R, Black S, Shinefield H, Lewis E, Ray P, Hansen J, et al. Safety of cold-adapted live attenuated influenza vaccine in a large cohort of children and adolescents. *Pediatric Infectious Disease Journal* 2004;**23**(2):138-44. [PUBMED: 14872180]

Brady 2014 *{published data only}*

Brady RC, Hu W, Houchin VG, Eder FS, Jackson KC, Hartel GF, et al. Randomized trial to compare the safety and immunogenicity of CSL Limited's 2009 trivalent inactivated influenza vaccine to an established vaccine in United States children. *Vaccine* 2014;**32**(52):7141-7. [PUBMED: 25454878]

Cuhaci 2012 *{published data only}*

Cuhaci CB, Beyazova U, Kemaloglu YK, Ozkan S, Gunduz B, Ozdek A. Effectiveness of pandemic influenza A/H1N1 vaccine

for prevention of otitis media in children. *European Journal of Pediatrics* 2012;**171**:1667-71.

Esposito 2003 *{published data only}*

Esposito S, Marchisio P, Cavagna R, Gironi S, Bosis S, Lambertini L, et al. Effectiveness of influenza vaccination of children with recurrent respiratory tract infections in reducing respiratory-related morbidity within the households. *Vaccine* 2003;**21**(23):3162-8.

Forrest 2008 *{published data only}*

Forrest BD, Pride MW, Dunning AJ, Capeding MR, Chotpitayasunondh T, Tam JS, et al. Correlation of cellular immune responses with protection against culture-confirmed influenza virus in young children. *Clinical and Vaccine Immunology* 2008;**15**(7):1042-53. [PUBMED: 18448618]

Gruber 1997 *{published data only}*

Gruber WC, Darden PM, Still JG, Lohr J, Reed G, Wright PF. Evaluation of bivalent live attenuated influenza A vaccines in children 2 months to 3 years of age: safety, immunogenicity and dose-response. *Vaccine* 1997;**15**(12-13):1379-84. [PUBMED: 9302748]

Han 2015 *{published data only}*

Han SB, Rhim JW, Shin HJ, Lee SY, Kim HH, Kim JH, et al. Immunogenicity and safety assessment of a trivalent, inactivated split influenza vaccine in Korean children: double-blind, randomized, active-controlled multicenter phase III clinical trial. *Human Vaccines & Immunotherapeutics* 2015;**11**(5):1094-102. [PUBMED: 25875868]

Heikkinen 1991 *{published data only}*

Heikkinen T, Ruuskanen O, Waris M, Ziegler T, Arola M, Halonen P. Influenza vaccination in the prevention of acute otitis media in children. *American Journal of Diseases of Children* 1991;**145**(4):445-8. [PUBMED: 1849344]

Houdouin 2016 *{published data only}*

Houdouin V, Lavis N, Meyzer C, Jeziorski E, Merlin E, Pinquier D, et al. Safety of the Northern Hemisphere 2014/2015 formulation of the inactivated split-virion intramuscular trivalent influenza vaccine. Vaccine Reports 2016; Vol. 6:1-7. [DOI: 10.1016/j.vacrep.2016.07.001]

Langley 2015 *{published data only}*

Langley JM, Wang L, Aggarwal N, Bueso A, Chandrasekaran V, Cousin L, et al. Immunogenicity and reactogenicity of an inactivated quadrivalent influenza vaccine administered intramuscularly to children 6 to 35 months of age in 2012-2013: a randomized, double-blind, controlled, multicenter, multicountry, clinical trial. *Journal of the Pediatric Infectious Diseases Society* 2015;**4**(3):242-51. [PUBMED: 26336604]

Loeb 2016 *{published data only}*

Loeb M, Russell ML, Manning V, Fonseca K, Earn DJ, Horsman G, et al. Live attenuated versus inactivated influenza vaccine in Hutterite children: a cluster randomized blinded trial. *Annals of Internal Medicine* 2016;**165**(9):617-24. [PUBMED: 27538259]

Longini 2000 *{published data only}*

Longini IM, Halloran ME, Nizam A, Wolff M, Mendelman PM, Fast PE, et al. Estimation of the efficacy of live, attenuated influenza vaccine from a two-year, multi-center vaccine trial: implications for influenza epidemic control. *Vaccine* 2000;**18**(18):1902-9. [PUBMED: 10699339]

Maeda 2004 *{published data only}*

Maeda T, Shintani Y, Nakano K, Terashima K, Yamada Y. Failure of inactivated influenza A vaccine to protect healthy children aged 6-24 months. *Pediatrics International* 2004;**46**(2):122-5. [PUBMED: 15056235]

Principi 2003 *{published data only}*

Principi N, Esposito S, Marchisio P, Gasparini R, Crovari P. Socioeconomic impact of influenza on healthy children and their families. *Pediatric Infectious Disease Journal* 2003;**22**(Suppl 10):207-10. [PUBMED: 14551476]

Thors 2016 *{published data only}*

Thors V, Christensen H, Morales-Aza B, Vipond I, Muir P, Finn A. The effects of live attenuated influenza vaccine on nasopharyngeal bacteria in healthy 2 to 4 year olds: a randomized controlled trial. *American Journal of Respiratory and Critical Care Medicine* 2016;**193**(12):1401-9. [PUBMED: 26742001]

Vesikari 2011 *{published data only}*

Vesikari T, Knuf M, Wutzler P, Karvonen A, Kieninger-Baum D, Schmitt HJ, et al. Oil-in-water emulsion adjuvant with influenza vaccine in young children. *New England Journal of Medicine* 2011;**365**(15):1406-16. [PUBMED: 21995388]

Additional references

Atkins 2004

Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. GRADE Working Group. Grading quality of evidence and strength of recommendations. *BMJ* 2004;**328**(7454):1490.

Bhatt 2011

Bhatt P, Block SL, Toback SL, Ambrose CS. Timing of the availability and administration of influenza vaccine through the vaccines for children program. *Pediatric Infectious Disease Journal* 2011;**30**(2):100-6. [PUBMED: 20686436]

Block 1995

Block SL, Harrison CJ, Hedrick JA, Tyler RD, Smith RA, Keegan E, et al. Penicillin-resistant Streptococcus pneumoniae in acute otitis media: risk factors, susceptibility patterns and antimicrobial management. *Pediatric Infectious Disease Journal* 1995;**14**(9):751-9. [PUBMED: 8559623]

Block 2011

Block SL, Heikkinen T, Toback SL, Zheng W, Ambrose CS. The efficacy of live attenuated influenza vaccine against influenza-associated acute otitis media in children. *Pediatric Infectious Disease Journal* 2011;**30**(3):203-7. [PUBMED: 20935591]

CDC 2011

Centers for Disease Control and Prevention. Prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP). Morbidity and Mortality Weekly Report (MMWR) 2011; Vol. 60, issue 33:1128-32.

DerSimonian 1986

DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled Clinical Trials* 1986;**7**:177-88.

Erdivanli 2012

Erdivanli OC, Coskun ZO, Kazikdas KC, Demirci M. Prevalence of otitis media with effusion among primary school children in Eastern Black Sea, in Turkey and the effect of smoking in the development of otitis media with effusion. *Indian Journal of Otolaryngology and Head and Neck Surgery* 2012;**64**(1):17-21. [PUBMED: 23449553]

Eskola 2001

Eskola J, Kilpi T, Palmu A, Jokinen J, Haapakoski J, Herva E, et al. Efficacy of a pneumococcal conjugate vaccine against acute otitis media. *New England Journal of Medicine* 2001;**344**(6):403-9. [PUBMED: 11172176]

Fireman 2003

Fireman B, Black SB, Shinefield HR, Lee J, Lewis E, Ray P. Impact of the pneumococcal conjugate vaccine on otitis media. *Pediatric Infectious Disease Journal* 2003;**22**(1):10-6. [PUBMED: 12544402]

Fortanier 2014

Fortanier AC, Venekamp RP, Boonacker CW, Hak E, Schilder AG, Sanders EA, et al. Pneumococcal conjugate vaccines for preventing otitis media. *Cochrane Database of Systematic Reviews* 2014, Issue 4. [DOI: 10.1002/14651858.CD001480.pub4]

GRADEpro 2014 [Computer program]

GRADE Working Group, McMaster University. GRADEpro GDT. Version (accessed 21 November 2015). Hamilton, ON: GRADE Working Group, McMaster University, 2014.

Grijalva 2006

Grijalva CG, Poehling KA, Nuorti JP, Zhu Y, Martin SW, Edwards KM, et al. National impact of universal childhood immunization with pneumococcal conjugate vaccine on outpatient medical care visits in the United States. *Pediatrics* 2006;**118**(3):865-73. [PUBMED: 16950975]

Heikkinen 2003

Heikkinen T, Chonmaitree T. Importance of respiratory viruses in acute otitis media. *Clinical Microbiology Reviews* 2003;**16**(2):230-41. [PUBMED: 12692096]

Heikkinen 2013

Heikkinen T, Block SL, Toback SL, Wu X, Ambrose CS. Effectiveness of intranasal live attenuated influenza vaccine against all-cause acute otitis media in children. *Pediatric Infectious Disease Journal* 2013;**32**:669-74.

Henderson 1982

Henderson FW, Collier AM, Sanyal MA, Watkins JM, Fairclough DL, Clyde WA Jr, et al. A longitudinal study of respiratory viruses and bacteria in the etiology of acute otitis media with effusion. *New England Journal of Medicine* 1982;**306**(23):1377-83. [PUBMED: 6281639]

Higgins 2011

Higgins JP, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Jacobs 1998

Jacobs MR, Dagan R, Appelbaum PC, Burch DJ. Prevalence of antimicrobial-resistant pathogens in middle ear fluid: multinational study of 917 children with acute otitis media. *Antimicrobial Agents and Chemotherapy* 1998;**42**(3):589-95. [PUBMED: 9517937]

Jefferson 2012

Jefferson T, Rivetti A, Di Pietrantonj C, Demicheli V, Ferroni E. Vaccines for preventing influenza in healthy children. *Cochrane Database of Systematic Reviews* 2012, Issue 8. [DOI: 10.1002/14651858.CD004879.pub4; PUBMED: 22895945]

Jefferson 2014

Jefferson T, Di Pietrantonj C, Rivetti A, Bawazeer GA, Al-Ansary LA, Ferroni E. Vaccines for preventing influenza in healthy adults. *Cochrane Database of Systematic Reviews* 2014, Issue 3. [DOI: 10.1002/14651858.CD001269.pub5]

Kozyrskyj 2010

Kozyrskyj AL, Klassen TP, Moffatt M, Harvey K. Short-course antibiotics for acute otitis media. *Cochrane Database of Systematic Reviews* 2010, Issue 9. [DOI: 10.1002/14651858.CD001095.pub2]

Leach 2011

Leach AJ, Morris PS. Antibiotics for the prevention of acute and chronic suppurative otitis media in children. *Cochrane Database of Systematic Reviews* 2011, Issue 1. [DOI: 10.1002/14651858.CD004401.pub2]

Lefebvre 2011

Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins JP, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Lieberthal 2004

Lieberthal AS, Ganiats TG, Cox EO, Culpepper L, Mahoney M, Miller D, et al. Diagnosis and management of acute otitis media. *Pediatrics* 2004;**113**(5):1451-65. [PUBMED: 15121972]

Lieberthal 2013

Lieberthal AS, Carroll AE, Chonmaitree T, Ganiats TG, Hoberman A, Jackson MA, et al. The diagnosis and management of acute otitis media. *Pediatrics* 2013;**131**(3):e964-99. [PUBMED: 23439909]

Marom 2014

Marom T, Tan A, Wilkinson GS, Pierson KS, Freeman JL, Chonmaitree T. Trends in otitis media-related health care use in the United States, 2001-2011. *JAMA* 2014;**168**(1):68-75. [PUBMED: 24276262]

MeReC 2006

Acute otitis media. *MeReC Bulletin* 2006;**17**(3):9-11.

Monobe 2003

Monobe H, Ishibashi T, Nomura Y, Shinogami M, Yano J. Role of respiratory viruses in children with acute otitis media. *International Journal of Pediatric Otorhinolaryngology* 2003;**67**(7):801-6.

Poehling 2004

Poehling KA, Lafleur BJ, Szilagyi PG, Edwards KM, Mitchel E, Barth R, et al. Population-based impact of pneumococcal conjugate vaccine in young children. *Pediatrics* 2004;**114**(3):755-61. [PUBMED: 15342850]

Prutsky 2014

Prutsky GJ, Domecq JP, Elraiyah T, Prokop LJ, Murad MH. Assessing the evidence: live attenuated influenza vaccine in children younger than 2 years. A systematic review. *Pediatric Infectious Disease Journal* 2014;**33**:e106-15.

RevMan 2014 [Computer program]

Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager 5 (RevMan 5). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Siddartha 2012

Siddartha Bhat V, Bhandary SK, Shenoy V, Rashmi. Otitis media with effusion in relation to socio economic status: a community based study. *Indian Journal of Otolaryngology and Head and Neck Surgery* 2012;**64**(1):56-8. [PUBMED: 23449688]

Stratton 2011

Stratton K, Ford A, Rusch E, Clayton EW. Adverse Effects of Vaccines: Evidence and Causality. Institute of Medicine (IOM) of The National Academies Press, 2011.

Venekamp 2015

Venekamp RP, Sanders SL, Glasziou PP, Del Mar CB, Rovers MM. Antibiotics for acute otitis media in children. *Cochrane Database of Systematic Reviews* 2015, Issue 6. [DOI: 10.1002/14651858.CD000219.pub4]

Venekamp 2016

Venekamp RP, Burton MJ, van Dongen TM, van der Heijden GJ, van Zon A, Schilder AG. Antibiotics for otitis media with effusion in children. *Cochrane Database of Systematic Reviews* 2016, Issue 6. [DOI: 10.1002/14651858.CD009163.pub3]

Vergison 2010

Vergison A, Dagan R, Arguedas A, Bonhoeffer J, Cohen R, Dhooge I, et al. Otitis media and its consequences: beyond the earache. *Lancet Infectious Diseases* 2010;**10**(3):195-203. [PUBMED: 20185098]

Yano 2009

Yano H, Okitsu N, Hori T, Watanabe O, Kisu T, Hatagishi E, et al. Detection of respiratory viruses in nasopharyngeal secretions and middle ear fluid from children with acute otitis media. *Acta Oto-Laryngologica* 2009;**129**(1):19-24.

References to other published versions of this review

Kay 2005

Kay E, Ng K, Salmon A, Del Mar C. Influenza vaccines for preventing acute otitis media in infants and children. *Cochrane Database of Systematic Reviews* 2005, Issue 3. [DOI: 10.1002/14651858.CD010089]

Norhayati 2012

Norhayati MN, Azman MY, Ho JJ. Influenza vaccines for preventing acute otitis media in infants and children. *Cochrane Database of Systematic Reviews* 2012, Issue 9. [DOI: 10.1002/14651858.CD010089]

Norhayati 2015

Norhayati MN, Ho JJ, Azman MY. Influenza vaccines for preventing acute otitis media in infants and children. *Cochrane Database of Systematic Reviews* 2015, Issue 3. [DOI: 10.1002/14651858.CD010089.pub2]

CHARACTERISTICS OF STUDIES

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

Belshe 2000

Methods	Prospective, randomised, double-blind, placebo-controlled and multicentre trial
Participants	Healthy children aged 15 to 71 months at the time of initial vaccination in year 1 Year 1: 1602 (vaccine group: 1070, placebo group: 532) Year 2: 1358 (vaccine group: 917, placebo group: 441) Exclusion criteria: history of clinically significant hypersensitivity to eggs or children with underlying chronic illnesses

Belshe 2000 *(Continued)*

	Setting: healthcare setting
Interventions	Participants were randomised in a 2:1 ratio to receive vaccine or placebo and followed through the subsequent 2 influenza seasons. In year 1, participants at 8 of the 10 centres primarily received 2 doses of vaccine or placebo and a single dose at the other 2 centres. In year 2, participants received a single dose of vaccine or placebo. Intervention: CAIV-T was administered. Duration of follow-up: for year 1, initial vaccination was given during the period of September to November 1997 and revaccination from November to March 1998. Follow-up was done during the influenza season, i.e. November to March 1998. Hence, the follow-up period postvaccination was 7 months (September to March).
Outcomes	1. First episode of culture-confirmed influenza illness in each year 2. Diagnosed OM The case definition of febrile OM was any healthcare provider diagnosis of OM associated with fever (either thermometer-documented or not).
Notes	Declared funding from vaccine manufacturer

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Prospective, randomised, double-blind, placebo-controlled, and multicentre trial
Allocation concealment (selection bias)	Unclear risk	Prospective, randomised, double-blind, placebo-controlled, and multicentre trial
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "... subjects and staff remained blinded throughout the study"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	153 children (14.6%) from the vaccine group and 91 children (17.1%) from the placebo group dropped out, the reasons for which were not explained.
Selective reporting (reporting bias)	Low risk	Protocol was not available, but all expected outcomes were reported.
Other bias	Low risk	We identified no other biases.

Bracco 2009

Methods	Placebo-controlled, multicentre study conducted during the 2001 and 2002 influenza seasons at 35 sites in South Africa, Brazil, and Argentina
Participants	2821 children aged 6 to 36 months Exclusion criteria: serious chronic disease, immunosuppression or presence of an immunocompromised household member, receipt of any commercial or investigational influenza vaccine before enrolment, a documented history of hypersensitivity to any component of LAIV or placebo Year 1: mean (SD) age (months): 2 doses vaccine group (20.4/8.5); 1 dose vaccine and 1 dose saline placebo group (20.1/8.6); 2 doses excipient placebo group (20.6/8.3); 2 doses saline placebo group (20.1/8.3) Setting: healthcare setting
Interventions	In year 1: children were randomised to 1 of 4 regimens of 2 doses LAIV, a single-dose vaccine, excipient placebo, or saline placebo. In year 2: vaccine recipients were to receive 1 of vaccine, and placebo recipients were to receive saline placebo. Year 1: 2821 (2 doses vaccine: 944; 1 dose vaccine and 1 dose saline placebo: 935; 2 doses excipient placebo: 468; 2 doses saline placebo: 474) Year 2: 2054 (1 dose vaccine: 339 + 690 + 346; 1 dose vaccine: 935; 1 dose saline placebo: 337 + 342) The total volume of vaccine and both placebos was 0.2 mL administered intranasally (approximately 0.1 mL into each nostril). Duration of follow-up: 11 days after treatment in year 1 and 28 days after treatment in year 2
Outcomes	1. First episode of culture-confirmed influenza illness caused by community-acquired subtypes antigenically similar (same type, subtype, and serotype) to those contained in the vaccine during year 1 2. First episode of culture-confirmed influenza caused by community-acquired subtypes antigenically similar to those in the vaccine during year 2 3. First episode of culture-confirmed influenza caused by any community-acquired subtypes during year 1 and year 2 4. First and all episodes of AOM, including any AOM, AOM associated with culture-confirmed influenza virus antigenically similar to a vaccine strain, and AOM associated with fever 5. Lower respiratory tract infections: the first incidence of any pneumonia, radiographically confirmed pneumonia, bronchitis, bronchiolitis, etc. Hospitalisation associated with pneumonia and hospitalisation associated with radiographically confirmed pneumonia 6. Immunogenicity: response for each virus strain and differences in the immunogenicity response after 2 doses compared with 1 dose of live attenuated influenza vaccine 7. Safety: reactogenicity events and adverse events
Notes	The number of children with episodes of AOM was reported only for those receiving 2 doses or a single dose of vaccine during year 1, and a single dose of vaccine during year 2. The number of children with episodes of AOM receiving excipient placebo or saline placebo was not reported. We therefore did not include the findings for the primary outcome in the meta-analysis due to lack of data for comparison with the control group. Only the secondary outcomes of adverse events were included. Declared funding from vaccine manufacturer

Risk of bias

Bias	Authors' judgement	Support for judgement

Bracco 2009 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "... randomised (2:2:1:1) to one of four study groups according to a preprinted randomisation allocation list"
Allocation concealment (selection bias)	Low risk	Quote: "Because of a treatment allocation coding and labelling error in the second season ..." Comment: Allocation concealment was stated although not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Subjects and personnel evaluating vaccine efficacy and safety remained blinded throughout the entire study period"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	2821 children (88.2%) completed year 1 without major protocol violations, and 2202 children continued in year 2. Due to an unintended treatment allocation error, 1 treatment group randomised to LAIV–LAIV/LAIV received placebo rather than LAIV (LAIV–LAIV/placebo), and 1 treatment group randomised to placebo–placebo/placebo received LAIV rather than placebo (placebo–placebo/LAIV). As a result, the overall year 2 per-protocol population included 1364 children (42.6%).
Selective reporting (reporting bias)	Low risk	Part of the results were available as online Supplemental Digital Content.
Other bias	Low risk	We identified no other biases.

Clements 1995

Methods	Mentioned as a prospective cohort study. However, this study is better described as a randomised controlled trial because (1) intervention is given, and (2) randomisation is present.
Participants	186 children aged 6 months to 5 years from day-care centres Exclusion criteria: no known or suspected acute illness, cancer, or impairment of immunologic function; and had not received any medications known to suppress the immune system in the previous 2 months Setting: day-care centres in North Carolina, USA
Interventions	Group 1 (N = 94) received 1 (children from previous year) or 2 doses of 0.25 mL trivalent subvirion influenza virus vaccine Group 2 (N = 11) received 3rd dose of hepatitis B vaccine (0.25 mL) Group 3 (N = 55) received ear examination by parents' request Group 4 (N = 26) received ear examination Sex (male/female): vaccine group (42/52), control groups (47/45) Duration of follow-up: mid-November to December 1993 (period 1), January to mid-February 1993 (period 2: influenza period), mid-February to mid-March 1994 (period 3: end of observation period). Hence, the follow-up period was 5 months (November to March)

Clements 1995 *(Continued)*

Outcomes	The ear examination was coded as SOM if fluid only was seen on visual otoscopic examination. The ear examination was coded as AOM if redness and fluid were seen in the same ear on either side, if pus alone was seen on either side, and if both SOM and AOM were present. 1. Occurrence of AOM 2. Occurrence of SOM
Notes	Declared funding from vaccine manufacturer

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "... children were randomised "; "New participants could be randomised to receive (3:1) the flu shot or nothing, or ear examinations only" Comments: Method of random sequence generation was not described.
Allocation concealment (selection bias)	Unclear risk	Comment: Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Children in the previous study continued in the study in the same group (blinded) if they were ..." Comment: Children were initially randomised to receive influenza vaccine or hepatitis B vaccine. However, following the Advisory Committee on Immunization Practice, the recommendation to receive hepatitis B vaccine was changed. Children in the previous group therefore continued to be blinded, and new participants were randomised to receive either the influenza vaccine or ear examination.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The examiners were blinded to the category of the participants"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All children completed the study.
Selective reporting (reporting bias)	Low risk	Protocol was not available, but all expected outcomes were reported.
Other bias	Low risk	We identified no other biases.

Gruber 1996

Methods	Double-blind, placebo-controlled trial
Participants	182 healthy children aged 6 to 18 months of age Exclusion criteria: not reported Setting: vaccine evaluation units at Baylor College of Medicine, St Louis University, University of Rochester, Vanderbilt University, and University of Maryland, USA
Interventions	Vaccine groups (N = 136 + 2) consisted of H1N1 (N = 44), H3N2 (N = 45), bivalent (N = 47).

Gruber 1996 *(Continued)*

	Control group (N = 44) Live attenuated, cold-adapted monovalent and bivalent influenza or placebo was given by nose drops as a 0.5 mL dose. Duration of follow-up: recruitment and vaccination was done in the autumn of 1991 and followed up in winter 1991 to 1992. Hence, the follow-up period postvaccination was around 3 months.
Outcomes	1. Serologic responses: HAI, ELISA 2. Virologic studies 3. Respiratory illness 4. Otitis media
Notes	The primary outcome was observed within 10 days postvaccination, hence results were not suitable to be included in meta-analysis. Only outcomes of adverse events were included. Declared funding from vaccine manufacturer

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Double-blind, placebo-controlled trial
Allocation concealment (selection bias)	Unclear risk	Double-blind, placebo-controlled trial
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Researchers were blinded to the groups. Quote: "Subjects were randomised in a double-blind fashion to receive a single dose of cold adapted monovalent influenza vaccine, bivalent influenza vaccine or placebo"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were missing for 2 children (1.4%) from the vaccine group within 10 days of vaccination because the diary information was not available. Otherwise data were complete.
Selective reporting (reporting bias)	Low risk	Protocol was not available, but all expected outcomes were reported.
Other bias	Low risk	We identified no other biases.

Hoberman 2003

Methods	Randomised, parallel-group trial
Participants	786 children (411 in first cohort and 375 in second cohort) aged 6 to 24 months stratified into (1) prone to otitis media (2) attend day care First cohort: sex (male/female): vaccine group (128/145), control group (75/63) Second cohort: sex (male/female): vaccine group (139/113), control group (53/123)

Hoberman 2003 *(Continued)*

	Exclusion criteria: premature or had a craniofacial abnormality; had or were living with persons at high risk of influenza; neurologic disorder, history of tympanostomy tube insertion, hypersensitivity to egg protein or thimerosal; febrile illness or severe respiratory illness within the preceding 48 hours Setting: Children's Hospital of Pittsburgh, Pennsylvania, USA
Interventions	Intervention group (N = 525) received inactivated trivalent subvirion influenza vaccine intramuscularly. 513 received 2 doses (0.25 mL each) 4 weeks apart, and 12 received 1 dose. Control group (N = 261) received placebo intramuscularly. 252 received 2 doses (0.25 mL each) 4 weeks apart, and 9 received 1 dose. Duration of follow-up: for the first cohort, recruitment and vaccination were given during the period of October to November 1999 and followed up until March to November. Hence, the duration of follow-up postvaccination was between 6 months and 1 year. For the second cohort, recruitment and vaccination were given during the period of September to December 2000 and followed up until March 2001. Hence, the follow-up period postvaccination was 6 months.
Outcomes	Acute otitis media is defined as presence of purulent otorrhoea of recent onset not due to otitis externa or of middle ear effusion accompanied by 1 or more of the following: ear pain, marked redness of the tympanic membrane, and substantial bulging of the tympanic membrane. 1. Proportion of children who developed AOM 2. Monthly occurrence rate of AOM 3. Estimated proportion of time with middle ear effusion 4. Utilisation of selected healthcare and related resources
Notes	Declared funding from vaccine manufacturer

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomly assigned the children in blocks of nine, using a computer generated list. ... in a 2:1 ratio"
Allocation concealment (selection bias)	Unclear risk	Randomised, parallel-group trial
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Assignments to treatment groups were not revealed to parents, investigators, research personnel conducting clinical follow-up, or non-study health care providers, all of whom remained blinded throughout the study" "Administration was performed by non-blinded research nurses who were not involved in subsequent clinical follow-up of the children." "Randomization lists were kept in locked files not accessible to blinded personnel"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "In the subjects in which otoscopic and tympanometric findings presented ambivalency or inconsistency, visual otoscopy was re-performed by another physician (any of the authors of this study) in a blind manner, and then tympanometry was repeated"
Incomplete outcome data (attrition bias) All outcomes	Low risk	27 children (5.1%) from the vaccine group and 11 children (4.2%) from the placebo group were excluded from the study. Reasons were provided. Intention-to-treat analysis was applied.

Hoberman 2003 *(Continued)*

Selective reporting (reporting bias)	Low risk	Protocol was not available, but all expected outcomes were reported.
Other bias	Low risk	We identified no other biases.

Kosalaraksa 2015

Methods	Randomised, placebo-controlled, observer-blinded study
Participants	838 children (6 months to 17 years at the time of first vaccination) Exclusion criteria: previous receipt of H5N1 vaccine; receipt of seasonal influenza vaccine within 14 days (inactivated vaccine) or 30 days (live vaccine); receipt of any vaccine not foreseen by the protocol up to 42 days from baseline; receipt of any investigational or non-registered product from 30 days before to 42 days after study vaccination; any significant acute or chronic uncontrolled illness; temperature of ≥ 38°C (≥ 100.4°F) at baseline assessment; cancer diagnosis within previous 3 years; immunosuppressive or immunodeficient conditions; receipt of glucocorticoids within 1 month of the start of and throughout the study; receipt of cytotoxic, immunosuppressive drugs within 6 months of the start of and throughout the study; receipt of immunoglobulins within 3 months of the start of and throughout the study; and history of allergy to influenza vaccine Setting: USA (N = 450), Canada (N = 96), and Thailand (N = 292)
Interventions	Randomisation ratio was 8:3 for vaccine to placebo, with equal allocation between 3 age strata. 1. 6 to 35 months (N = 199 vaccine group, N = 75 control group, N = 274 total) 2. 3 to 8 years (N = 198 vaccine group, N = 76 control group, N = 274 total) 3. 9 to 17 years (N = 210 vaccine group, N = 80 control group, N = 290 total) Assessment of immunogenicity: at days 0, 21, and 42; for half of the children in each age strata at day 182, and for the other half at day 385 Assessment of reactogenicity: at day 7 postvaccination Assessment safety: up to 1 year after vaccination Intervention group (N = 607) received 2 doses of H5N1 influenza vaccine (AS03B-adjuvanted H5N1 A/Indonesia/5/2005 with antigen produced in Quebec). Control group (N = 231) received 2 doses of placebo (0.25 mL of saline). Vaccine or placebo injections were administered in the non-dominant (dose 1) and dominant arm (dose 2) 21 days apart. Duration of follow-up: 1 year
Outcomes	Immunogenicity objectives were to assess: 1. haemagglutination inhibition antibody titers against the vaccine strain; 2. haemagglutination inhibition antibody responses against the vaccine strain; 3. whether responses fulfilled the immunogenicity licensure criteria; 4. virus neutralising antibody responses against the vaccine strain and drifted strain. Reactogenicity objectives were to assess: 1. solicited local symptoms; 2. general symptoms. Safety objectives were to assess:

Kosalaraksa 2015 *(Continued)*

1. unsolicited adverse events;
2. serious adverse events;
3. medically attended adverse events;
4. potential immune-mediated diseases.

Notes	Prospective registration: ClinicalTrials.gov identifier: NCT01310413 (first received 24 February 2011) We contacted the authors and obtained further information from the clinical trials register via Clinical Study Data Request. We have reported only the results of general symptoms, namely febrile illness, drowsiness, irritability/fussiness, and loss of appetite, for all children aged less than 6 years (N = 294 vaccine group, N = 122 control group, N = 416 total). Declared funding from vaccine manufacturer

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed using a blocking scheme ..."
Allocation concealment (selection bias)	Unclear risk	Quote: "... treatment allocation at study sites was done using an Internet-based system" Note: Not described. If the recruiting personnel understood the blocking scheme used, it might be possible to predict the next patient.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Participants and study personnel involved in the collection and analysis of data were blinded to treatment."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "... study personnel involved in the collection and analysis of data were blinded to treatment."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were missing for 42 participants (565/607, 93.1%) from the vaccine group and for 14 participants (217/231, 93.9%) from the control group at day 385. Missing data were evenly balanced across the 2 groups.
Selective reporting (reporting bias)	Low risk	Protocol available. All prespecified outcomes reported in final report. All expected outcomes were reported.
Other bias	Low risk	We identified no other biases.

Lum 2010

Methods	Prospective, randomised, double-blind, placebo-controlled, multicentre, phase III study conducted over an influenza season at 32 sites in 13 countries (Bangladesh, Belgium, Finland, Germany, Hong Kong, Lithuania, Malaysia, Mexico, the Philippines, Poland, Singapore, South Korea, and Thailand)
Participants	1120 healthy children aged 11 to less than 24 months Mean (SD) age (months): vaccine group (14.4/3.0), placebo group (14.4/3.2) Sex (male/female): vaccine group (383/364), placebo group (175/189)

Lum 2010 *(Continued)*

	Exclusion criteria: serious chronic disease, including progressive neurologic disease, Down syndrome or other cytogenetic disorder or known or suspected disease of the immune system, received aspirin or aspirin-containing products 2 weeks before immunisation, and documented history of hypersensitivity to egg or egg protein Surveillance for influenza-like illness and the decision to obtain a nasal swab sample were based on information obtained through weekly telephone contacts, clinic visits, or home visits. Setting: healthcare setting
Interventions	2 intranasal doses of trivalent LAIV or placebo were given 35 ± 7 days apart. LAIV + combined measles, mumps, and rubella vaccine, live, attenuated (Priorix): 747 children Placebo + Priorix: 373 children Duration of follow-up: recruitment and vaccination were done during a 3-week period from 4 October 2002 and followed up until 31 May 2003. Follow-up began on the 11th day after receipt of the first dose of study treatment and continued for around 8 months over 1 full influenza season (until 31 May 2003).
Outcomes	1. Immune response 2. Efficacy of LAIV - culture-confirmed influenza Acute otitis media was defined by a visually abnormal tympanic membrane concomitant with at least 1 of the following: fever, earache, irritability, diarrhoea, vomiting, acute otorrhoea not caused by external otitis or other symptoms of respiratory infection. An episode of AOM was diagnosed as a new episode if at least 30 days had elapsed since the previous episode, regardless of aetiology.
Notes	Declared funding from vaccine manufacturer

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Subjects were randomised 2:1 (LAIV:placebo) to receive 2 doses of LAIV or placebo 35 ± 7 days apart using a randomisation schedule generated by Wyeth Vaccines Research. Participants were assigned a treatment using an interactive voice recognition system"
Allocation concealment (selection bias)	Low risk	Quote: "All subjects received open-label Priorix administered concomitantly with the first dose of LAIV or placebo. Study subjects, their parents / legal guardians and study clinical personnel were not aware of whether LAIV or placebo was co administered with Priorix"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Study subjects, their parents / legal guardians and study clinical personnel were not aware of whether LAIV or placebo was co administered with Priorix. There were no instances in which subjects were unblinded until after the completion of the study"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	72 children (8.8%) from the vaccine group and 41 children (9.9%) from the placebo group were excluded from the study. Reasons were provided. Intention-to-treat analysis was applied.
Selective reporting (reporting bias)	Low risk	Protocol was not available, but all expected outcomes were reported.

Lum 2010 *(Continued)*

Other bias	Low risk	We identified no other biases.

Marchisio 2002

Methods	Randomised, parallel-group trial
Participants	133 children aged 1 to 5 years with a history of recurrent AOM (defined as ≥ 3 episodes in the preceding 6 months or ≥ 4 episodes in the preceding 12 months, with the most recent episode of AOM in the previous 2 to 8 weeks) Mean (SD) age (months): vaccine group (32.6/14.6), control group (36.2/15.9) Sex (male/female): vaccine group (38/29), control group (42/24) Exclusion criteria: acute febrile illness, severe atopy, any previous influenza vaccination, acquired or congenital immunodeficiency, recent administration of blood products, cleft palate, chronically ruptured eardrum, obstructive adenoids, sleep apnoea syndrome, and placement of tympanostomy tubes Setting: healthcare setting, Italy
Interventions	Intervention group (N = 67) received 2 doses of intranasal, inactivated, virosomal subunit influenza vaccine on day 1 and day 8. Control group (N = 66) received no treatment. Duration of follow-up: every 4 to 6 weeks for 25 weeks
Outcomes	Acute otitis media was based on the presence of any combination of: fever, earache, irritability, and hyperaemia or opacity accompanied by bulging or immobility of the tympanic membrane. Otitis media with effusion was based on the presence of impaired mobility, opacification, fullness, or retraction of the eardrum associated with a tympanogram with a flat tracing, and the absence of signs and symptoms of acute infection. 1. Occurrence of AOM within the 6-month period 2. Occurrence of febrile respiratory illnesses 3. Use of antibiotics
Notes	Declared funding from vaccine manufacturer

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "... assigned randomly" Comments: Method of random sequence generation was not described.
Allocation concealment (selection bias)	Unclear risk	Quote: "... assignment and vaccine administration were performed by two investigators"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "... the parents were instructed not to discuss group assignment with the investigator responsible for the clinical and ontological follow-up, who remained blinded to group assignment until the end of the follow-up period" Comment: We judged this to be of low risk for all outcomes except participant-reported adverse effects.

Marchisio 2002 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "... the investigator responsible for the clinical and ontological follow-up, who remained blinded to group assignment until the end of the follow-up period"
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 children (3.0%) from the vaccine group and 5 children (7.6%) from the placebo group did not complete the study. Reasons were provided. Intention-to-treat analysis was carried out.
Selective reporting (reporting bias)	Low risk	Protocol was not available, but all expected outcomes were reported.
Other bias	Low risk	We identified no other biases.

Swierkosz 1994

Methods	Randomised controlled trial
Participants	22 healthy children aged 2 to 22 months Setting: not reported, USA
Interventions	Intervention group (N = 17) received 3 doses (0.5 mL each) of CAIV intranasally 60 days apart. Control group (N = 5) received placebo. Exclusion criteria: not reported Duration of follow-up: clinical observation was followed up for 11 days, and serum for antibody determinations was obtained 30 to 60 days postvaccination.
Outcomes	Immunogenicity
Notes	Primary outcome was not included in the meta-analysis due to short follow-up period. Only outcomes for adverse events were included.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Subjects were randomised to receive vaccine or placebo in a double-blinded way. One of every three or four children received placebo"
Allocation concealment (selection bias)	Unclear risk	Randomised controlled trial
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Subjects were randomised to receive vaccine or placebo in a double-blinded way. One of every three or four children received placebo"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	Data were not reported for 2 children (11.8%) from the vaccine group and 2 children (40.0%) from the placebo group at day 60, and 2 children (23.5%)

Swierkosz 1994 *(Continued)*

		from the vaccine group and 4 children (80.0%) from the placebo group at day 120. The reasons were not provided and the group losses were > 20%.
Selective reporting (reporting bias)	Low risk	Protocol was not available, but all expected outcomes were reported.
Other bias	Low risk	We identified no other biases.

Tam 2007

Methods	Prospective, randomised, double-blind, placebo-controlled, multicentre, cross-over trial conducted during 2 consecutive years at 16 sites in 8 regions (China, Hong Kong, India, Malaysia, the Philippines, Singapore, Taiwan, and Thailand)
Participants	Healthy children aged 12 to 36 months Mean (SD) age (months): vaccine group (23.6/7.4), placebo group (23.4/7.3) Year 1: sex (male/female): vaccine group (880/773), placebo group (588/523) (per-protocol population) Exclusion criteria: serious chronic disease, including progressive neurologic disease; Down syndrome or other cytogenetic disorder, or known or suspected disease of the immune system; and those with documented history of hypersensitivity to egg or egg protein Setting: healthcare setting
Interventions	In year 1, children were randomised 3:2 (CAIV-T:placebo) to receive 2 doses of CAIV-T or 2 doses of placebo. In year 2, children were re-randomised in a 1:1 ratio to receive a single dose of CAIV-T or placebo without consideration of their group assignment in the first year. Year 1 (N = 3174): intervention group (N = 1900) received 2 doses (0.2 mL each) of CAIV-T 28 days apart. Control group (N = 1274) received saline placebo. Year 2 (N = 2947): intervention group (N = 1900) received 1 dose of CAIV-T. Control group (N = 1274) received saline placebo. Duration of follow-up: follow-up began on the 11th day after receipt of the first dose of study treatment and continued for 2 years.
Outcomes	1. Efficacy 2. Safety
Notes	Acute otitis media cases were too few, and hence were not reported in the study. Additionally, the duration of follow-up is less than 6 months. Only outcomes of adverse events were included. Declared funding from vaccine manufacturer

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Subjects were randomised 3:2 (CAIV-T:placebo) to receive two doses of CAIV-T or two doses of placebo at least 28 days apart using a randomisation schedule generated by Wyeth. In year 2, subjects were re-randomised in a 1:1 ratio to receive a single dose of CAIV-T or placebo without consideration of their group assignment in the first year."

Tam 2007 *(Continued)*

		Quote: "The randomisation schedule for each year was generated by Wyeth Vaccines Research ... using an interactive voice response system ... numbered according to a predetermined randomisation list"
Allocation concealment (selection bias)	Low risk	Quote: "Both CAIV-T and placebo were supplied in identically packaged sprayers; neither the study subjects, their parents/guardians, or the clinical personnel were aware of the treatment being administered"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Both CAIV-T and placebo were supplied in identically packaged sprayers; neither the study subjects, their parents/guardians, or the clinical personnel were aware of the treatment being administered"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	In year 1, 247 children (13.0%) from the vaccine group and 163 children (12.8%) from the control group, and in year 2, 203 children (13.7%) from the vaccine group and 217 children (14.8%) from the control group dropped out. Reasons were provided. Intention-to-treat analysis was applied in both years.
Selective reporting (reporting bias)	Low risk	Protocol was not available, but all expected outcomes were reported.
Other bias	Low risk	We identified no other biases.

Vesikari 2006

Methods	Prospective, randomised, double-blind, placebo-controlled, multicentre trial conducted over 2 consecutive influenza seasons at 70 clinical centres located in Belgium, Finland, Israel, Spain, and the UK between 2 October 2000 and 31 May 2002 Setting: healthcare setting
Participants	1616 children aged 6 to 36 months who attended day care Exclusion criteria: serious chronic disease, Down syndrome or other cytogenetic disorders, documented history of hypersensitivity to egg or egg protein, immunosuppression or a household member with immunosuppression, received immunoglobulin in the past 6 months or investigational agent 1 month before enrolment; influenza treatment or aspirin or clinically confirmed respiratory illness or wheezing 2 weeks before enrolment Year 1: 1616 children (vaccine: 951, placebo: 665 children) Mean (SD) age (months): vaccine group (23.3/8.0), placebo group (23.5/7.8) Sex (male/female): vaccine group (496/455), placebo group (337/328) Year 2: 1090 children (vaccine: 640, placebo: 450 children) Mean (SD) age (months): vaccine group (23.5/7.9), placebo group (23.7/7.8) Sex (male/female): vaccine group (341/299), placebo group (219/231)
Interventions	The total single-dose volume of 0.2 mL (0.1 mL into each nostril) of LAIV or placebo was administered intranasally with the spray applicator. Placebo consisted of sterile physiologic saline solution. The first dose of the primary series was administered on day 0.

Vesikari 2006 *(Continued)*

	Duration of follow-up: in year 1, study treatment was administered by December 2000. Follow-up began on the 11th day after receipt of the first dose of study treatment and continued until May 2001. In year 2, study treatment was administered by December 2001. Follow-up began on the 11th day after receipt of the first dose of study treatment and continued until May 2002. Hence, the follow-up period postvaccination for both year 1 and year 2 was 6 months.
Outcomes	Acute otitis media was defined as a visually abnormal tympanic membrane (with regard to colour, position, and/or mobility) suggesting an effusion in the middle ear cavity, concomitant with 1 of the following signs and/or symptoms of acute infection: fever (rectal temperature of 38°C or axillary temperature of 37.5°C), earache, irritability, diarrhoea, vomiting, acute otorrhoea not caused by external otitis, or other symptoms of respiratory infection. Influenza-associated AOM was defined as an episode of AOM in a child with a positive culture for influenza virus that occurred ≥ 15 days after receipt of the first dose of vaccine or placebo, during the period in which influenza virus was isolated in each country. 1. Safety 2. Tolerability 3. Efficacy 4. Effectiveness - antibiotic use
Notes	Declared funding from vaccine manufacturer

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Subjects were assigned randomly to receive a primary series of two doses of either CAIV-T or placebo, in a 3:2 ratio ... In year 2, all participants received a single dose of either CAIV-T or placebo according to their year 1 treatment assignments" Quote: "The randomisation schedule was generated by Wyeth Vaccines Research. Study product for year 1 was labelled with 1 of five letter codes, namely, A, H, or M (CAIV-T) or B or K (placebo). Each subject was assigned the next sequential number by the study site investigator and received study product for the treatment assigned to that subject number, according to a preprinted randomisation allocation list provided to the study site by Wyeth Vaccines Research"
Allocation concealment (selection bias)	Low risk	Quote: "... study subjects, their parents or guardians, and the clinical personnel were unaware of the treatment being administered. CAIV-T and placebo were supplied in single-dose, identically packaged sprayers labelled with the codes to which subjects were assigned"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The randomisation schedule was generated by Wyeth Vaccines Research. Study product for year 1 was labelled with 1 of five letter codes, namely, A, H, or M (CAIV-T) or B or K (placebo). Each subject was assigned the next sequential number by the study site investigator and received study product for the treatment assigned to that subject number, according to a preprinted randomisation allocation list provided to the study site by Wyeth Vaccines Research"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	1735 children (97.3%) completed year 1; of the 49 children (2.7%) who withdrew during year 1, most did so at parental request (1.2%) or were lost to fol-

Vesikari 2006 *(Continued)*

		low-up monitoring (1.0%). 4 children (2 in the CAIV-T group and 2 in the placebo group) withdrew during year 1 because of adverse effects. In year 2, 1119 children who completed year 1 successfully (i.e. received both doses of study vaccine according to the protocol) received a single dose of the same treatment they had received in year 1. A total of 1112 children (99.4%) completed the study; 7 children (1 in the CAIV-T group and 6 in the placebo group) were lost to follow-up monitoring during year 2. No children withdrew from the study in year 2 because of adverse effects. An additional 22 children (17 in the CAIV-T group and 5 in the placebo group) were excluded from the efficacy analysis in year 2 because of major protocol violations. Intention-to-treat analysis was applied.
Selective reporting (reporting bias)	Low risk	Protocol was not available, but all expected outcomes were reported.
Other bias	Low risk	We identified no other biases.

AOM: acute otitis media
CAIV: cold-adapted influenza vaccine
CAIV-T: trivalent cold-adapted influenza vaccine
ELISA: enzyme-linked immunosorbent assay
HAI: haemagglutination antibody inhibition
LAIV: live attenuated influenza vaccine
OM: otitis media
OME: otitis media with effusion
SD: standard deviation
SOM: serous otitis media

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

Study	Reason for exclusion
Ashkenazi 2006	Compares efficacy and safety of cold-adapted influenza vaccine, trivalent with trivalent inactivated influenza vaccine. Involved 2187 children aged 6 to 71 months old. No placebo or intervention control group included.
Belshe 1998	Compares efficacy of vaccine and placebo based on viral cultures for influenza. Involved 1602 children aged 15 to 71 months old. No related primary or secondary outcome measures
Belshe 2007	Compares efficacy of cold-adapted trivalent live attenuated influenza vaccine and trivalent inactivated vaccine. Involved 8352 children aged 6 to 59 months old. No placebo or intervention control group included. No related primary or secondary outcome measures
Bergen 2004	Compares safety of single-dose cold-adapted influenza vaccine and placebo. Involved 5637 children aged 1 to 8 years old. The medical adverse events were reported for otitis media, pharyngitis, and febrile illness. However, data for the number or proportion of children aged less than 6 years were not available after contacting the authors.
Brady 2014	Compares safety and immunogenicity between trivalent inactivated influenza vaccine and the US-licensed influenza vaccine. There was no placebo group.

Study	Reason for exclusion
Cuhaci 2012	Compares monovalent influenza vaccine and unvaccinated control groups. Involved 92 children aged 6 to 60 months old. Excluded for quasi-randomisation. Reported primary outcome but follow-up for 4 to 8 weeks only.
Esposito 2003	Compares respiratory-related morbidity between inactivated, trivalent, virosome-formulated subunit influenza vaccine and placebo. Involved 127 children aged 6 months to 9 years. No related primary or secondary outcome measures
Forrest 2008	Compares cell-mediated immunity responses between 3 dose levels of vaccine and saline placebo. Involved 2172 children aged 6 to less than 36 months old. No related primary or secondary outcome measures
Gruber 1997	Compares serologic responses between cold-adapted influenza vaccine and placebo. Involved 1126 children aged 2 to 36 months old. No related primary or secondary outcome measures
Han 2015	Compares immunogenicity and safety between single dose and two doses of influenza vaccine. There was no placebo group.
Heikkinen 1991	Compares incidence of acute otitis media between vaccine and control. Involved 374 children aged 1 to 3 years old. Excluded for quasi-randomisation. Reported primary outcome but follow-up for 6 weeks only.
Houdouin 2016	Compares the potential increases in reactogenicity and allergic events of Northern Hemisphere 2014/2015 formulation of the inactivated split-virion intramuscular trivalent influenza vaccine (Vaxigrip) and historical data. No placebo or intervention control group included.
Langley 2015	Compares immunogenicity and reactogenicity between quadrivalent and trivalent influenza vaccine. Involved 601 children aged 6 to 35 months old. There was no placebo group.
Loeb 2016	Compares effectiveness of vaccination between intranasal live attenuated influenza vaccine and inactivated influenza vaccine based on reverse transcriptase polymerase chain reaction-confirmed influenza A or B virus. Involved 4611 children and adolescents aged 36 months to 15 years old. There was no placebo group.
Longini 2000	Compares efficacy between cold-adapted influenza vaccine and placebo based on viral cultures for influenza. Involved 1601 children aged 15 to 71 months old. No related primary or secondary outcome measures
Maeda 2004	Compares the prophylactic effect between inactivated influenza vaccine and control. Involved 346 children aged 6 to 24 months. No related primary or secondary outcome measures
Principi 2003	Compares socioeconomic impact of vaccine and control. Involved 303 children aged 6 months to 5 years old. No related primary or secondary outcome measures
Thors 2016	Compares nasopharyngeal bacterial colonisation between live attenuated influenza vaccine and control. Involved 151 children. No related primary or secondary outcome measures
Vesikari 2011	Compares the efficacy of trivalent inactivated influenza vaccine with or without the presence of an oil-in-water emulsion of adjuvant MF59. Involved 4707 children aged 6 to 72 months old. No related primary or secondary outcome measures

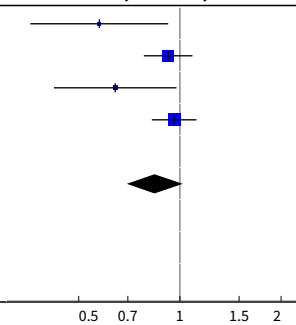
DATA AND ANALYSES

Comparison 1. Influenza vaccine versus control

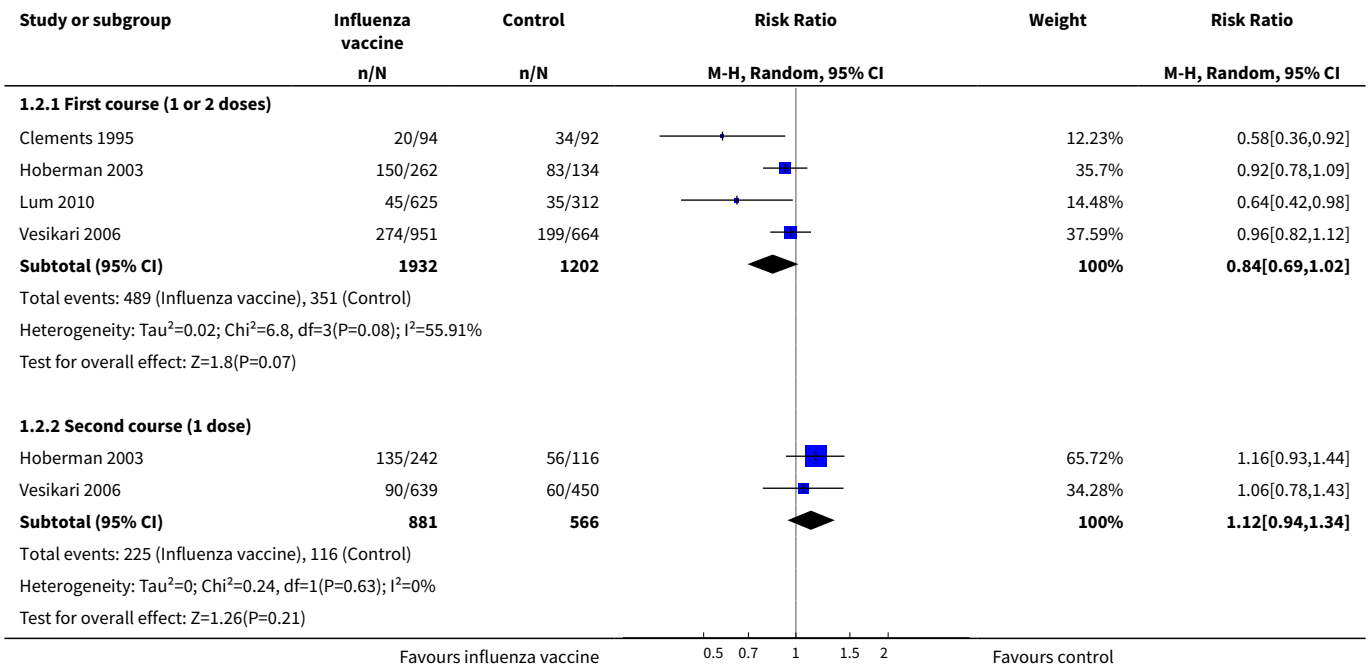
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 At least 1 episode of acute otitis media	4	3134	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.69, 1.02]
2 Acute otitis media by courses	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 First course (1 or 2 doses)	4	3134	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.69, 1.02]
2.2 Second course (1 dose)	2	1447	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.94, 1.34]
3 Acute otitis media by type of vaccine	4	3134	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.69, 1.02]
3.1 Trivalent cold-adapted influenza vaccine	2	2552	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.56, 1.21]
3.2 Trivalent sub virion influenza vaccine	2	582	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.48, 1.23]
4 Courses of antibiotics	2	1223	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.59, 0.83]
5 Fever	7	10615	Risk Ratio (M-H, Random, 95% CI)	1.15 [1.06, 1.24]
6 Rhinorrhoea	6	10563	Risk Ratio (M-H, Random, 95% CI)	1.17 [1.07, 1.29]
7 Pharyngitis	3	4429	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.80, 1.25]

Analysis 1.1. Comparison 1 Influenza vaccine versus control, Outcome 1 At least 1 episode of acute otitis media.

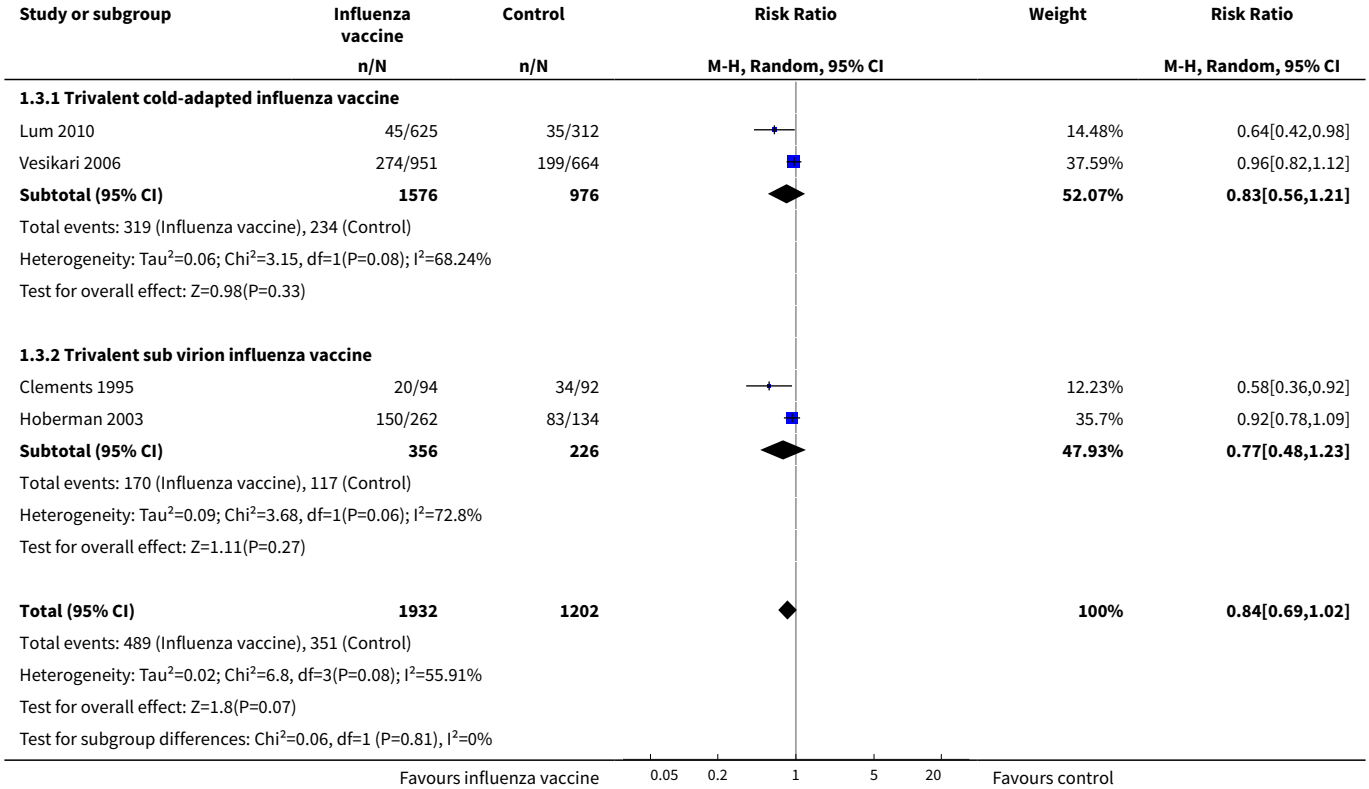
Study or subgroup	Influenza vaccine n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Clements 1995	20/94	34/92		12.23%	0.58[0.36,0.92]
Hoberman 2003	150/262	83/134		35.7%	0.92[0.78,1.09]
Lum 2010	45/625	35/312		14.48%	0.64[0.42,0.98]
Vesikari 2006	274/951	199/664		37.59%	0.96[0.82,1.12]
Total (95% CI)	**1932**	**1202**		**100%**	**0.84[0.69,1.02]**
Total events: 489 (Influenza vaccine), 351 (Control)					
Heterogeneity: Tau^2=0.02; Chi^2=6.8, df=3(P=0.08); I^2=55.91%					
Test for overall effect: Z=1.8(P=0.07)					



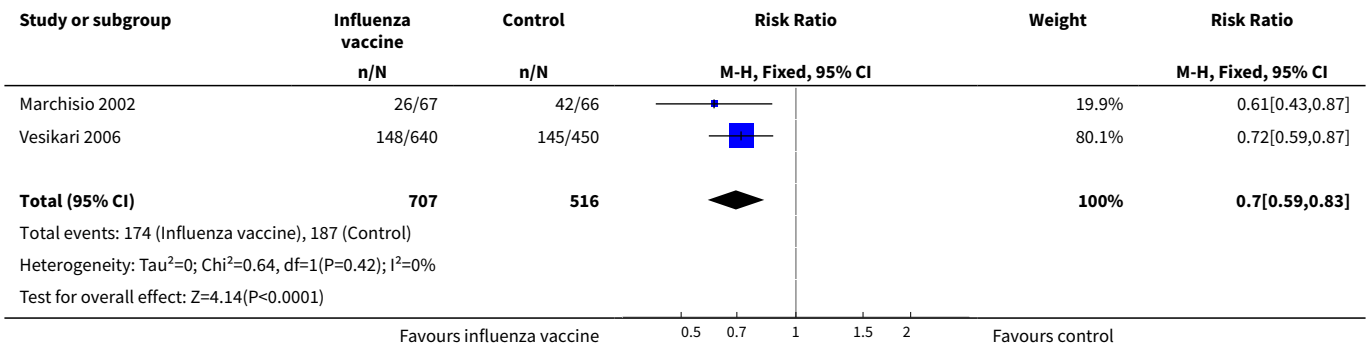
Analysis 1.2. Comparison 1 Influenza vaccine versus control, Outcome 2 Acute otitis media by courses.



Analysis 1.3. Comparison 1 Influenza vaccine versus control, Outcome 3 Acute otitis media by type of vaccine.

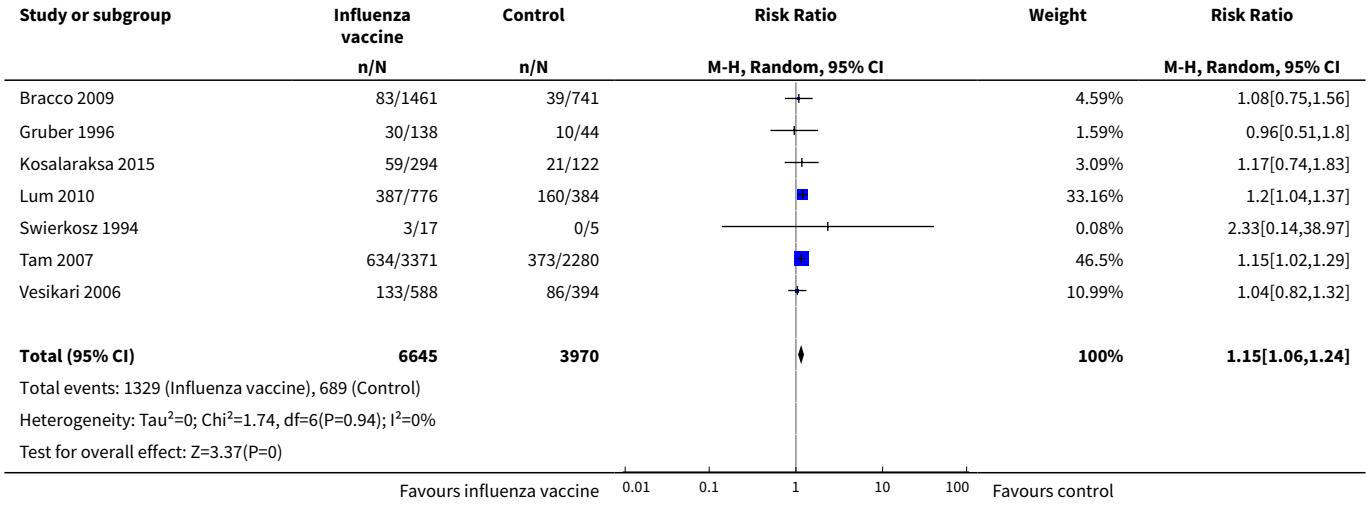


Analysis 1.4. Comparison 1 Influenza vaccine versus control, Outcome 4 Courses of antibiotics.



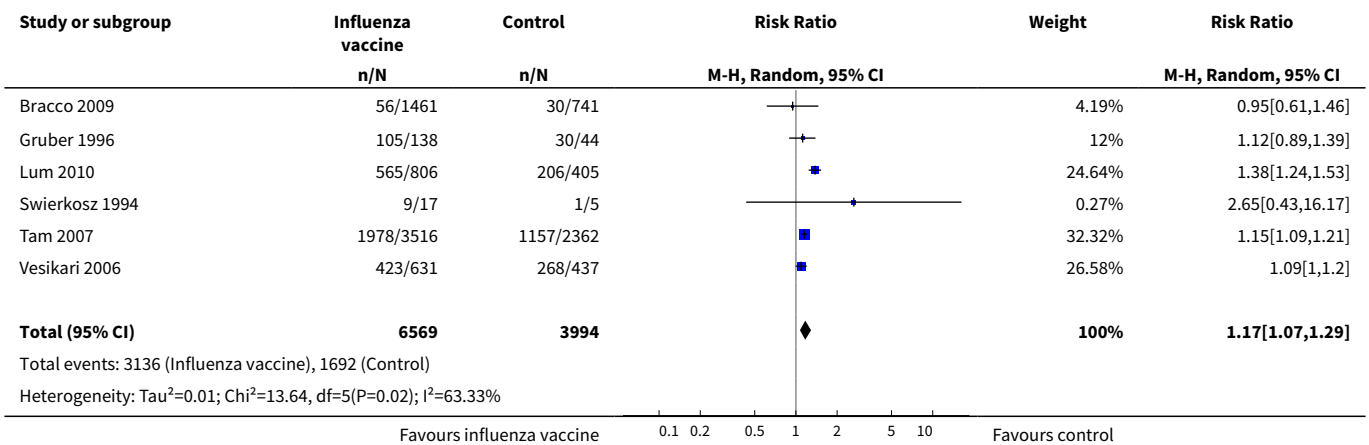
Study or subgroup	Influenza vaccine n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Marchisio 2002	26/67	42/66		19.9%	0.61[0.43,0.87]
Vesikari 2006	148/640	145/450		80.1%	0.72[0.59,0.87]
Total (95% CI)	**707**	**516**		**100%**	**0.7[0.59,0.83]**
Total events: 174 (Influenza vaccine), 187 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.64, df=1(P=0.42); I^2=0%					
Test for overall effect: Z=4.14(P<0.0001)					

Analysis 1.5. Comparison 1 Influenza vaccine versus control, Outcome 5 Fever.

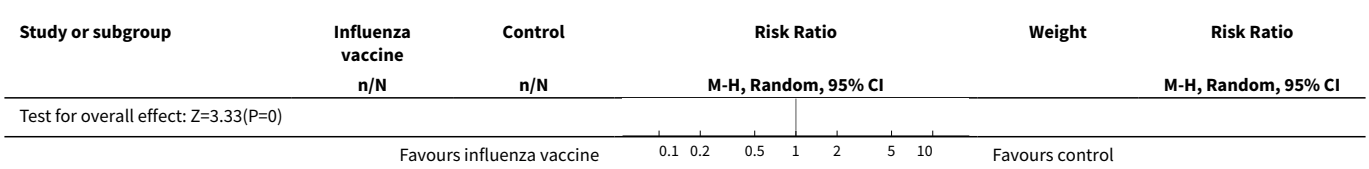


Study or subgroup	Influenza vaccine n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Bracco 2009	83/1461	39/741		4.59%	1.08[0.75,1.56]
Gruber 1996	30/138	10/44		1.59%	0.96[0.51,1.8]
Kosalaraksa 2015	59/294	21/122		3.09%	1.17[0.74,1.83]
Lum 2010	387/776	160/384		33.16%	1.2[1.04,1.37]
Swierkosz 1994	3/17	0/5		0.08%	2.33[0.14,38.97]
Tam 2007	634/3371	373/2280		46.5%	1.15[1.02,1.29]
Vesikari 2006	133/588	86/394		10.99%	1.04[0.82,1.32]
Total (95% CI)	**6645**	**3970**		**100%**	**1.15[1.06,1.24]**
Total events: 1329 (Influenza vaccine), 689 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.74, df=6(P=0.94); I^2=0%					
Test for overall effect: Z=3.37(P=0)					

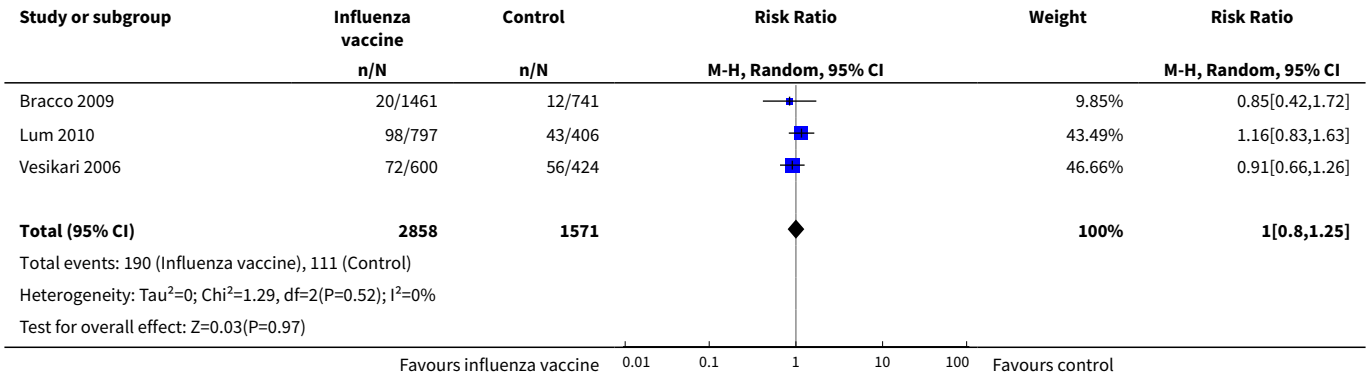
Analysis 1.6. Comparison 1 Influenza vaccine versus control, Outcome 6 Rhinorrhoea.



Study or subgroup	Influenza vaccine n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Bracco 2009	56/1461	30/741		4.19%	0.95[0.61,1.46]
Gruber 1996	105/138	30/44		12%	1.12[0.89,1.39]
Lum 2010	565/806	206/405		24.64%	1.38[1.24,1.53]
Swierkosz 1994	9/17	1/5		0.27%	2.65[0.43,16.17]
Tam 2007	1978/3516	1157/2362		32.32%	1.15[1.09,1.21]
Vesikari 2006	423/631	268/437		26.58%	1.09[1,1.2]
Total (95% CI)	**6569**	**3994**		**100%**	**1.17[1.07,1.29]**
Total events: 3136 (Influenza vaccine), 1692 (Control)					
Heterogeneity: Tau^2=0.01; Chi^2=13.64, df=5(P=0.02); I^2=63.33%					



Analysis 1.7. Comparison 1 Influenza vaccine versus control, Outcome 7 Pharyngitis.



APPENDICES

Appendix 1. MEDLINE (Ovid) search strategy

1 exp Otitis Media/
2 otitis media.tw.
3 (OM or OME or AOM or CSOM).tw.
4 glue ear*.tw.
5 (middle ear* adj5 (infect* or inflam*)).tw.
6 or/1-5
7 exp influenzavirus a/ or exp influenzavirus b/ or influenzavirus c/
8 Influenza, Human/
9 (influenza* or flu).tw.
10 or/7-9
11 exp Vaccines/
12 exp Vaccination/
13 (laiv or tiv).tw.
14 exp Immunization/
15 (vaccin* or immuni* or innocul*).tw.
16 or/11-15
17 10 and 16
18 Viral Vaccines/
19 Influenza Vaccines/
20 or/17-19
21 6 and 20

Appendix 2. Embase (Elsevier) search strategy

#27 #18 AND #26
#26 #21 NOT #25
#25 #22 NOT #24
#24 #22 AND #23
#23 'human'/de

#22 'animal'/de OR 'nonhuman'/de OR 'animal experiment'/de
#21 #19 OR #20
#20 random*:ab,ti OR placebo*:ab,ti OR crossover*:ab,ti OR 'cross over':ab,ti OR allocat*:ab,ti OR trial:ti OR (doubl* NEXT/1 blind*):ab,ti
#19 'randomised controlled trial'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp
#18 #5 AND #17
#17 #15 OR #16
#16 'virus vaccine'/de OR 'influenza vaccine'/de
#15 #9 AND #14
#14 #10 OR #11 OR #12 OR #13
#13 laiv:ab,ti OR tiv:ab,ti
#12 vaccin*:ab,ti OR immuni*:ab,ti OR inocul*:ab,ti
#11 'immunization'/exp
#10 'vaccine'/exp
#9 #6 OR #7 OR #8
#8 influenza*:ab,ti OR flu:ab,ti
#7 'influenza'/exp
#6 'influenza virus'/de OR 'influenza virus a'/exp OR 'influenza virus b'/de OR 'influenza virus c'/de
#5 #1 OR #2 OR #3 OR #4
#4 ('middle ear' NEAR/5 (infect* OR inflam*)):ab,ti OR ('middle ears' NEAR/5 (infect* OR inflam*)):ab,ti
#3 'glue ear':ab,ti OR 'glue ears':ab,ti
#2 'otitis media':ab,ti OR om:ab,ti OR ome:ab,ti OR aom:ab,ti OR csom:ab,ti
#1 'otitis media'/exp

Appendix 3. CINAHL (EBSCO) search strategy

S32 S22 and S31
S31 S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30
S30 (MH "Quantitative Studies")
S29 TI placebo* OR AB placebo*
S28 (MH "Placebos")
S27 TI random* OR AB random*
S26 TI ((singl* or doubl* or tripl* or trebl*) W1 (blind* or mask*)) OR AB ((singl* or doubl* or tripl* or trebl*) W1 (blind* or mask*))
S25 TI clinic* trial* OR AB clinic* trial*
S24 PT clinical trial
S23 (MH "Clinical Trials+")
S22 S6 and S21
S21 S18 or S19 or S20
S20 (MH "Influenza Vaccine")
S19 (MH "Viral Vaccines")
S18 S12 and S17
S17 S13 or S14 or S15 or S16
S16 TI (laiv or tiv) OR AB (laiv or tiv)
S15 TI (vaccin* or immuni* or inocul*) OR AB (vaccin* or immuni* or inocul*)
S14 (MH "Immunization+")
S13 (MH "Vaccines+")
S12 S7 or S8 or S9 or S10 or S11
S11 TI (influenza* or flu) OR AB (influenza* or flu)
S10 (MH "Influenza+")
S9 (MH "Influenzavirus C")
S8 (MH "Influenzavirus B+")
S7 (MH "Influenzavirus A+")
S6 S1 or S2 or S3 or S4 or S5
S5 TI (middle ear* N5 (infect* or inflam*)) OR AB (middle ear* N5 (infect* or inflam*))
S4 TI glue ear* OR AB glue ear*
S3 TI (OM or OME or AOM or CSOM) OR AB (OM or OME or AOM or CSOM)
S2 TI otitis media OR AB otitis media
S1 (MH "Otitis Media+")

Appendix 4. LILACS (BIREME) search strategy

> Search > (MH:"Otitis Media" OR MH:C09.218.705.663$ OR "otitis media" OR "Otite Média" OR "glue ear" OR "glue ears" OR OME OR AOM OR CSOM OR OM OR "middle ear infection" OR "middle ear infections" OR "middle ear inflammation") AND (MH:"Influenza Vaccines" OR MH:D20.215.894.899.302 OR "Vacunas contra la Influenza" OR "Vacinas contra Influenza" OR "Vacunas contra Gripe" OR

"Vacunas Antigripales" OR "Vacinas Antigripais" OR MH:"Viral Vaccines" OR MH:D20.215.894.899$ OR "Vacunas Virales" OR "Vacinas Virais" OR (MH:Vaccines OR Vacunas OR Vacinas OR MH:D20.215.894$ OR MH:Immunization OR Inmunización OR Imunização OR MH:E02.095.465.425.400$ OR MH:E05.478.550$ OR MH:N02.421.726.758.310$ OR MH:N06.850.780.200.425$ OR MH:N06.850.780.680.310$ OR MH:SP2.026.182.113$ OR SP4.001.002.015.049$ OR SP8.946.819.838$ OR "Estimulación Inmunológica" OR Inmunoestimulación OR "Sensibilización Inmunológica" OR Variolación OR Variolización OR Inmunizaciones OR "Estimulação Imunológica" OR Imunoestimulação "Sensibilização Imunológica" OR Variolação OR Imunizações OR vaccin$ OR immuni$ OR inocul$ OR laiv OR tiv) AND (MH:"Influenza, Human" OR Gripe OR Grippe OR influenza$ OR flu OR MH:"Influenzavirus A" OR MH:B04.820.545.405$ OR MH:B04.909.777.545.405$ OR MH:"Influenzavirus B" OR MH:B04.820.545.407$ OR MH:B04.909.777.545.407$ OR MH:"Influenzavirus C")) > clinical_trials

Appendix 5. Web of Science (Thomson Reuters) search strategy

# 5	#4 AND #3 *Databases=SCI-EXPANDED, CPCI-S Timespan=All Years* *Lemmatization=On*
# 4	Title=(trial) OR Topic=(random* or placebo* or ((singl* or doubl*) NEAR/1 blind*) or rct or "clinical trial") *Databases=SCI-EXPANDED, CPCI-S Timespan=All Years* *Lemmatization=On*
# 3	#2 AND #1 *Databases=SCI-EXPANDED, CPCI-S Timespan=All Years* *Lemmatization=On*
# 2	Topic=(influenza* or flu) AND Topic=(vaccin* or immuni* or inocul* or laiv or tiv) *Databases=SCI-EXPANDED, CPCI-S Timespan=All Years* *Lemmatization=On*
# 1	Topic=("otitis media" OR "glue ear" OR "glue ears" OR ("middle ear" NEAR/5 (infect* or inflam*))) *Databases=SCI-EXPANDED, CPCI-S Timespan=All Years* *Lemmatization=On*

FEEDBACK

Feedback, 7 December 2016

Summary

In this review, the results presented for the outcome 'courses of antibiotics' are confusing. Analysis 1.6 gives 187/516 (influenza vaccine) versus 174/707 (control group), which is about 36% versus 25%, i.e. an 11% reduction. These same figures are given in the Summary of

Findings table. However, in the abstract and in the Plain Language Summary, a Risk Difference of 0.15 is reported (which would be 15%). Is it 11% or 15%?

I do not have any affiliation with or involvement in any organisation with a financial interest in the subject matter of my comment

Hans van der Wouden
Affiliation: EMGO-VUmc Amsterdam-Netherlands
Role: Senior researcher, Cochrane review author, Editor of the ARI Group

Reply

We agree that you are right. It is 11%. Thank you.

Contributors

Mohd N Norhayati

WHAT'S NEW

Date	Event	Description
15 February 2017	New search has been performed	We updated our searches in February 2017 and identified one new trial for inclusion (Kosalaraksa 2015). We excluded one trial that was previously awaiting classification, Bergen 2004, and six new trials identified in the updated search (Brady 2014; Han 2015; Houdouin 2016; Langley 2015; Loeb 2016; Thors 2016). We added three analyses for adverse events, i.e. drowsiness, irritability/fussiness, and loss of appetite, in the text.
15 February 2017	New citation required but conclusions have not changed	Our conclusions remain unchanged.
15 February 2017	Feedback has been incorporated	Feedback received and response incorporated.

CONTRIBUTIONS OF AUTHORS

Designing the review: Mohd N Norhayati (MNN), Mohd Y Azman (MYA), and Jacqueline J Ho (JJH).
Co-ordinating the review: MNN.
Literature search: MNN, MYA.
Quality assessment: MNN, MYA. For this update MNN, JJH.
Entering data into Review Manager 5: MNN.
Data analysis: JJH, MNN.
Data interpretation: JJH, MNN.
Writing the review: MNN, JJH, MYA.

DECLARATIONS OF INTEREST

Mohd N Norhayati: none known.
Jacqueline J Ho: none known.
Mohd Y Azman: none known.

SOURCES OF SUPPORT

Internal sources

- Universiti Sains Malaysia, Malaysia.
- Penang Medical College, Malaysia.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We included a subgroup analysis for otitis media episodes by season, as we think there might be a difference in the outcome for vaccine administered during the influenza and the broader respiratory season. We removed the types of influenza vaccine from our secondary outcomes, deciding this was better included as a subgroup analysis. Neither of these subgroup analyses were stated in the protocol. For this update, we did not perform the subgroup analyses for trial setting and season due to the small number of trials in the subgroups. We removed Belshe 2000 from the analyses of primary outcomes (courses of vaccine and types of vaccine) because it reported episodes per person, and there was no measure of dispersion. We did not perform a subgroup analysis for utilisation of healthcare due to the limited number of trials involved. We did not do a subgroup analysis by type of adverse event. We have reported each type of adverse event as a separate analysis.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Anti-Bacterial Agents [therapeutic use]; Influenza Vaccines [adverse effects] [*therapeutic use]; Otitis Media [*prevention & control]; Randomized Controlled Trials as Topic

MeSH check words

Child, Preschool; Humans; Infant