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[Intervention Review]

Vaccines for preventing influenza in healthy children

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ABSTRACT

Background

The consequences of influenza in children and adults are mainly absenteeism from school and work. However, the risk of complications is greatest in children and people over 65 years of age.

Objectives

To appraise all comparative studies evaluating the effects of influenza vaccines in healthy children, assess vaccine efficacy (prevention of confirmed influenza) and effectiveness (prevention of influenza-like illness (ILI)) and document adverse events associated with influenza vaccines.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2011, Issue 3) which includes the Acute Respiratory Infections Group's Specialised Register, OLD MEDLINE (1950 to 1965), MEDLINE (1966 to November 2011), EMBASE (1974 to November 2011), Biological Abstracts (1969 to September 2007), and Science Citation Index (1974 to September 2007).

Selection criteria

Randomised controlled trials (RCTs), cohort and case-control studies of any influenza vaccine in healthy children under 16 years of age.

Data collection and analysis

Four review authors independently assessed trial quality and extracted data.

Main results

We included 75 studies with about 300,000 observations. We included 17 RCTs, 19 cohort studies and 11 case-control studies in the analysis of vaccine efficacy and effectiveness. Evidence from RCTs shows that six children under the age of six need to be vaccinated with live attenuated vaccine to prevent one case of influenza (infection and symptoms). We could find no usable data for those aged two years or younger.

Inactivated vaccines in children aged six years or older are not significantly more efficacious than placebo. Twenty-eight children over the age of six need to be vaccinated to prevent one case of influenza (infection and symptoms). Eight need to be vaccinated to prevent

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one case of influenza-like-illness (ILI). We could find no evidence of effect on secondary cases, lower respiratory tract disease, drug prescriptions, otitis media and its consequences and socioeconomic impact. We found weak single-study evidence of effect on school absenteeism by children and caring parents from work. Variability in study design and presentation of data was such that a meta-analysis of safety outcome data was not feasible. Extensive evidence of reporting bias of safety outcomes from trials of live attenuated influenza vaccines (LAIVs) impeded meaningful analysis. One specific brand of monovalent pandemic vaccine is associated with cataplexy and narcolepsy in children and there is sparse evidence of serious harms (such as febrile convulsions) in specific situations.

Authors' conclusions

Influenza vaccines are efficacious in preventing cases of influenza in children older than two years of age, but little evidence is available for children younger than two years of age. There was a difference between vaccine efficacy and effectiveness, partly due to differing datasets, settings and viral circulation patterns. No safety comparisons could be carried out, emphasising the need for standardisation of methods and presentation of vaccine safety data in future studies. In specific cases, influenza vaccines were associated with serious harms such as narcolepsy and febrile convulsions. It was surprising to find only one study of inactivated vaccine in children under two years, given current recommendations to vaccinate healthy children from six months of age in the USA, Canada, parts of Europe and Australia. If immunisation in children is to be recommended as a public health policy, large-scale studies assessing important outcomes, and directly comparing vaccine types are urgently required. The degree of scrutiny needed to identify all global cases of potential harms is beyond the resources of this review.

This review includes trials funded by industry. An earlier systematic review of 274 influenza vaccine studies published up to 2007 found industry-funded studies were published in more prestigious journals and cited more than other studies independently from methodological quality and size. Studies funded from public sources were significantly less likely to report conclusions favourable to the vaccines. The review showed that reliable evidence on influenza vaccines is thin but there is evidence of widespread manipulation of conclusions and spurious notoriety of the studies. The content and conclusions of this review should be interpreted in the light of this finding.

PLAIN LANGUAGE SUMMARY

Vaccines for preventing influenza in healthy children

Children (< 16 years old) and the elderly (above 65 years old) are the two age groups that appear to have the most complications following an influenza infection. Influenza has a viral origin and often results in an acute respiratory illness affecting the lower or upper parts of the respiratory tract, or both. Viruses are mainly of two subtypes (A or B) and spread periodically during the autumn-winter months. However, many other viruses can also cause respiratory tract illnesses.

Diffusion and severity of the disease could be very different during different epidemics. Efforts to contain epidemic diffusion rely mainly on widespread vaccination. Recent policy from several internationally-recognised institutions, recommend immunisation of healthy children between 6 and 23 months of age (together with their contacts) as a public health measure.

The review authors found that in children aged from two years, nasal spray vaccines made from weakened influenza viruses were better at preventing illness caused by the influenza virus than injected vaccines made from the killed virus. Neither type was particularly good at preventing 'flu-like illness' caused by other types of viruses. In children under the age of two, the efficacy of inactivated vaccine was similar to placebo. It was not possible to analyse the safety of vaccines from the studies due to the lack of standardisation in the information given, but very little information was found on the safety of inactivated vaccines, the most commonly used vaccine in young children.

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BACKGROUND

Description of the condition

Influenza is an acute respiratory illness that affects the upper and/or lower parts of the respiratory tract and is caused by an influenza virus, usually of type A or B. In temperate climates, influenza generally affects people from November to March in the Northern Hemisphere and from May to September in the Southern Hemisphere. It can occur all year round in tropical climates. Influenza epidemics may take place from time to time, although the extent and severity of such epidemics varies widely.

Description of the intervention

There are four types of influenza vaccines currently available worldwide:

1. Whole virion inactivated vaccines which consist of complete viruses which have been 'killed' or inactivated, so that they are not infectious but retain their strain-specific antigenic properties.
2. Subunit inactivated vaccines which are made of influenza surface antigens (H and N) only.
3. Split virion inactivated vaccines in which the viral structure is broken up by a disrupting agent. These vaccines contain both surface and internal antigens.
4. Live attenuated, cold-adapted vaccines in which the live virus in the vaccine can only multiply in the cooler nasal passages and which are administered intranasally.

Periodic antigenic drifts and shifts pose problems for vaccine production and procurement. New vaccines closely matching the antigenic configuration of circulating strains must be produced and procured for the beginning of each new influenza 'season'. To achieve this, the World Health Organization (WHO) has established a worldwide surveillance system allowing early identification and isolation of viral strains circulating in the different parts of the world.

How the intervention might work

Efforts to prevent the spread of influenza have shown to be unsuccessful due to the infectiousness of the condition, and public health interventions rely on vaccination to mitigate the worst consequences of the disease (death and hospitalisation).

Most high-income countries have vaccination programmes covering the elderly and the so-called at 'risk groups' (for example, people with pre-existing conditions likely to be made worse by influenza infection). However, for the influenza season 2004 to 2005, the American Academy of Pediatrics and the US Centers for Disease Control and Prevention (CDC) recommended that immunisation of healthy children aged between 6 and 23 months be instituted as a public health measure (AAPCID 2004). This was later extended to cover children aged 6 to 59 months (i.e. six months to five years) (CDC 2007) and to healthy household contacts (including children) and caregivers of children aged under five years (CDC 2007). In February 2004, the Canadian National Advisory Committee on Immunization followed the US authorities in recommending immunisation for the 6 to 23 months age group (Orr 2004).

Finland is the only European country to have introduced routine vaccination of children aged six months to three years (from the beginning of the 2007 to 2008 influenza season). Other countries have also recommended childhood vaccination but have not included it in the routine childhood programmes. Slovenia and Latvia recommended vaccination of children aged six months to two years. Slovakia, Estonia and Austria recommended it for children and adolescents aged six months to 18 years (Mereckiene 2010).

Why it is important to do this review

The main arguments for immunising young children (Izurieta 2000; Neuzil 2000; Principi 2004) and those attending school (Principi 2004; Reichert 2001) include:

1. reduction of the number of patients with influenza;
2. reduction in the number of admissions to hospital;
3. reduction in mortality of the elderly in families with children;
4. reduction in illness in health care workers; and
5. reduction in the number of antibiotic prescriptions and the reduction in absenteeism of children from school and their parents or carers or household contacts from work.

Rational decision-making about the prevention of influenza is complicated by absence of reliable forecasts, uncertainty about the effects of the vaccine in different age groups and the vaccines efficacy versus effectiveness issue. Cochrane Reviews on the effects of the use of vaccines to prevent influenza in other age and risk groups show a striking difference between the vaccine efficacy (reduction in number of laboratory-confirmed cases of influenza) and vaccine effectiveness against influenza-like illness (ILI) (reduction in symptomatic cases), which can include illness caused by influenza viruses that is not laboratory-confirmed or illness caused by other viruses, such as respiratory syncytial virus (RSV). To allow a reasoned choice between alternative prevention strategies, accurate assessment of both the efficacy and effectiveness of influenza vaccines is essential. The aim of this review is to identify, assess and compare studies of vaccine efficacy and vaccine effectiveness in healthy children under 16 years of age, and review the safety of vaccines in children up to 16 years of age.

OBJECTIVES

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- To identify and appraise all the comparative studies evaluating the effects of influenza vaccines in healthy children under 16 years of age.

- To assess the efficacy of vaccines in preventing influenza in healthy children.

- To assess the effectiveness of vaccines in preventing ILI in healthy children.

- To document the types and frequency of adverse effects associated with influenza vaccines in healthy children.

METHODS

Criteria for considering studies for this review

Types of studies

We considered randomised controlled trials (RCTs), quasi-randomised, comparative controlled trials (CCTs) and cohort and case-controlled studies. For study design definitions see Appendix 1. We decided to include evidence from comparative non-randomised studies to enhance the relevance of the review.

Types of participants

Healthy children under 16 years of age in any geographical location. All participants were classified as healthy unless otherwise stated. We excluded studies which documented the inclusion of participants with chronic illnesses/conditions or immunodeficiency.

Types of interventions

Vaccination with any influenza vaccine given independently, in any dose, preparation or time schedule (intervention), compared with placebo, or with no intervention (control).
We also considered newer, or as yet unlicensed types of vaccines (for example, live attenuated and DNA vaccines).

Types of outcome measures

Primary outcomes

Primary outcome measures for treatment efficacy and effectiveness

1. Influenza: symptoms of influenza accompanied by a positive laboratory diagnosis (measure of vaccine efficacy).
2. Influenza-like-illness (ILI): symptoms of influenza only (measure of vaccine effectiveness).
3. Otitis media.
4. Lower respiratory tract diseases.
5. Cases admitted to hospital:
    i) hospitalisation due to otitis media
6. Deaths of study participants (either from influenza or other causes).

Primary outcome measures for adverse events

1. All types of systemic and severe adverse events.

Secondary outcomes

Secondary outcome measures for treatment efficacy and effectiveness

1. Direct or indirect indicator of disease impact:
    i) working day lost (WDL) for influenza;
    ii) school absenteeism for influenza;
    iii) drug prescriptions; and
    iv) outpatients attendances.

Secondary outcome measures for adverse events

1. All types of local adverse events.

Search methods for identification of studies

Electronic searches

For this update we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2011, Issue 3; www.thecochranelibrary.com) (accessed on November 16th, 2011), which includes the Acute Respiratory Infections Group's Specialised Register, MEDLINE (1966 to November 2011), and EMBASE (1974 to November 2011). See Appendix 2 for details of previous searches.
We used the following search terms to search PUBMED. We adapted the search terms to search CENTRAL (Appendix 3) and EMBASE (Appendix 4).

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No.	Query
#1	"Influenza Vaccines"[MeSH] OR("Influenza, Human/complications"[MeSH]OR"Influenza,Human/epidemiology"[MeSH]OR"Influenza, Human/immunology"[MeSH] OR "Influenza, Human/mortality"[MeSH] OR "Influenza, Human/prevention and control"[MeSH] OR "Influenza, Human/transmission"[MeSH])
#2	((influenza vaccin*[Text Word]) OR ((influenza [Text Word] OR flu[Text Word]) AND (vaccin*[Text Word] OR immuni*[Text Word] OR inocula*[Text Word] OR efficacy[Text Word] OR effectiveness[Text Word])))
#3	#1 OR #2
#4	(randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab])
#5	("cross over" OR "crossover" OR "Follow Up") OR ("Cross-Over Studies"[MeSH] OR "Follow-Up Studies"[MeSH] OR "Prospective Studies"[MeSH]) OR ("time series" OR "interrupted time series") OR (placebo* OR random* OR "double blind" OR "single blind" OR clinical trial* OR trial design) OR ("Case-Control Studies"[MeSH] OR (cases[Title/Abstract] AND controls[Title/Abstract])) OR ("Cohort Studies"[MeSH] OR cohort*) OR ("Comparative Study"[Publication Type]) OR ("before after"[Title/Abstract] OR "before-after"[Title/Abstract] OR "before/after"[Title/Abstract] OR "before and after"[Title/Abstract]) OR (volunteer*[Title/Abstract]) OR (control*[Text Word] AND evaluation[Text Word]) OR (longitudinal[Text Word]) OR (retrospective*[Text Word])
#6	#4 OR #5
#7	#3 AND #6
#8	#3 AND #6 Limits: All Child: 0-18 years
#9	child* OR preschool* OR school* OR young OR adolescent* OR infant* OR toddler* OR pediatric* OR paediatric* OR infant*
#10	#7 AND #9
#11	#8 OR #10

We did not impose any language or publication restrictions.

Searching other resources

To identify additional published and unpublished studies we searched the Vaccine Adverse Event Reporting System Website (http://www.vaers.org). We contacted vaccine manufacturers and first or corresponding authors of relevant studies to identify further published or unpublished trials.

Data collection and analysis

Selection of studies

Two review authors (TOJ, AR) independently excluded all studies not fulfilling the inclusion criteria of initially identified and retrieved articles. In the case of disagreement, arbitration was carried out by VD.

Data extraction and management

Four review authors (AR, TOJ, CDP, EF) performed data extraction using a data extraction form (Appendix 5). We checked the

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data and entered it into Review Manager 5 (RevMan 2011) software. We extracted data on the following:

- methodological quality of studies;
- study design (Appendix 1);
- description of setting;
- characteristics of participants;
- description of vaccines (content and antigenic match);
- description of outcomes;
- publication status;
- date of study; and
- location of study.

One review author (CDP) carried out statistical analyses.

Assessment of risk of bias in included studies

Experimental studies (trials)

The review authors independently assessed the methodological quality of the included studies using criteria from the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). In the case of disagreement in assigning quality criteria amongst the review authors (TOJ, EF, CDP, AR), VD carried out arbitration. We classified studies for assessing risk of bias according to the following key domains (Higgins 2011).

Generation of the allocation sequence

- Low risk of bias: if for example, a table of random numbers or computer-generated random numbers were used.
- High risk of bias: if for example, alternation, date of birth, day of the week, or case record number were used.
- Unclear risk of bias: if no sufficient information was provided.

Allocation concealment

- Low risk of bias: if for example, numbered or coded identical containers administered sequentially, on-site computer system that can only be accessed after entering the characteristics of an enrolled participant, or serially numbered, opaque, sealed envelopes, were used, or sealed envelopes that are not sequentially numbered or opaque were used.
- High risk of bias: if for example, open table of random numbers were used.
- Unclear risk of bias: if no sufficient information was provided.

Blinding

- Low risk of bias: if adequate double-blinding, for example, placebo vaccine, were used, or single-blind, that is to say, blinded outcome assessment, were used.
- High risk of bias; if no blinding.
- Unclear risk of bias: if no sufficient information was provided.

Incomplete outcome data

Number of losses to follow-up.

- Low risk of bias: no missing data, or the proportion of missing data compared with observed event risk was not enough to have a clinically relevant impact on the intervention effect estimate.
- High risk of bias: the proportion of missing data compared with observed event risk was enough to induce clinically relevant bias in intervention effect estimate.
- Unclear risk of bias: if no sufficient information was provided.

Non-experimental studies

We assessed the quality of non-randomised studies in relation to the presence of potential confounders, which could make interpretation of the results difficult. We evaluated the quality of case-control (prospective and retrospective) and cohort studies using the appropriate Newcastle-Ottawa Scales (NOS) (Appendix 6). Using quality at the analysis stage as a means of interpretation of the results, we assigned risk of bias categories (Higgins 2011) as:

1. low risk of bias: plausible bias unlikely to seriously alter the results;
2. unclear risk of bias: plausible bias that raises some doubt about the results; and
3. high risk of bias: plausible bias that seriously weakens confidence in the results.

Measures of treatment effect

We used the risk ratio (RR) and its 95% confidence interval (CI) as the summary measure. We calculated vaccine efficacy (or effectiveness) as VE = 1 - RR expressed as a percentage, for cohort and RCT/CCT studies. For case-control studies we adopted the odds ratio (OR) with 95% CIs.

To enhance relevance to everyday practice, we also expressed the summary measure of the most reliable and significant comparisons (those from RCTs with influenza cases as an outcome by age group) as a risk difference (RD). This is a measure of absolute efficacy of the vaccines which incorporates significant information such as the incidence in the control arm and allows the calculation of its reciprocal, the number needed to treat (in this case, vaccinate or NNV). NNV expresses the number of children needed to be

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vaccinated to prevent one case of influenza. There was insufficient evidence to calculate meaningful RDs for rarer outcomes (such as hospitalisations or pneumonia), or the evidence was of poor quality (as in the case of cohorts).

Unit of analysis issues

For cluster-randomised trials we did not compute effective sample size as described by Higgins 2011 because information supplied by papers was insufficient to compute intracluster correlation (ICC) and additional information was not available. However, for aa Alexandrova 1986, aa Rudenko 1993a, aa Rudenko 1993b, aa Rudenko 1996a and aa Rudenko 1996b, average cluster size was big enough to suppose a very small ICC and a design effect close to 1 (Higgins 2011). Also for aa Clover 1991 and aa Gruber 1990 information about intracluster correlation was unavailable. Nevertheless, even if we suppose for these studies an ICC different from zero, we have to take into account that average cluster size is small and that we expect a design effect close to 1. Because of the small sample size of each arm, we can suppose that the reduction to effective sample size was negligible.
We summarised evidence from non-randomised studies (cohort and case-control) in our review according to Higgins 2011.

Dealing with missing data

Our analysis relied on existing data. Whenever possible we used the intention-to-treat (ITT) population.

Assessment of heterogeneity

We calculated the I^2 statistic for each pooled estimate, to assess the impact on statistical heterogeneity. The I^2 statistic may be interpreted as the proportion of total variation among effect estimates that is due to heterogeneity rather than sampling error, and it is intrinsically independent of the number of studies. When the I^2 is < 30% there is little concern about statistical heterogeneity (Higgins 2011). We used random-effects models throughout to take account of the between-study variance in our findings (Higgins 2011). Variance is to be expected in influenza vaccine trials as there are unpredictable systematic differences between trials regarding the circulating strains, degree of antigenic matching of the vaccine, type of vaccine and the levels of immunity presented by different population in different settings. Not all studies reported sufficient details to enable a full analysis of the sources of heterogeneity, but we were able to take into account age group and number of doses.

Assessment of reporting biases

Due to the limited number of studies in each comparison, assessment of publication bias was not applicable.

The overall quality of retrieved studies was poor and was affected by poor reporting or limited descriptions of the studies' design. A detailed description is provided in the Quality of the evidence section of the review.

Data synthesis

We carried out data synthesis separately for live and inactivated vaccines. We grouped studies for analysis according to study design: trials, cohort studies, and case-controlled studies.
Between-trial variability is to be expected in influenza vaccine studies as there are unpredictable differences between effect estimates. Heterogeneity was incorporated into the pooled estimates by using the DerSimonian Laird random-effects model.
We used RRs of events for the comparisons of vaccine with placebo/control groups for RCTs and cohort studies; we used ORs for the single case-controlled study.

Subgroup analysis and investigation of heterogeneity

We carried out subgroup analyses by age group for trials, cohort and case-control studies, as follows: under two years (from 0 to 23 months); under six years (from 24 months to 6 years) and over six years of age. We selected the under two years of age group as the US CDC recommends vaccination for healthy children aged 6 to 23 months (CDC 2011; Fiore 2011; Harper 2004). The under six years and over six years categories reflected the most frequent stratification in primary studies. One comparison (Analysis 8), which includes rare outcomes, included both vaccine types (live and inactivated). However, we only considered the subgroup analyses.

Sensitivity analysis

We performed two sensitivity analyses, excluding studies translated from Russian (Table 1) and excluding studies with high risk of bias (Table 2).

RESULTS

Description of studies

Results of the search

From the searches we identified 8340 records, corresponding to 6519 citations (after duplicates were removed). We screened 6519 records and excluded 6332 records on the basis of the title and abstract. We retrieved 188 papers in full-text and excluded 102 (reasons are summarised in the Excluded studies section and the Characteristics of excluded studies tables). Finally we included 75

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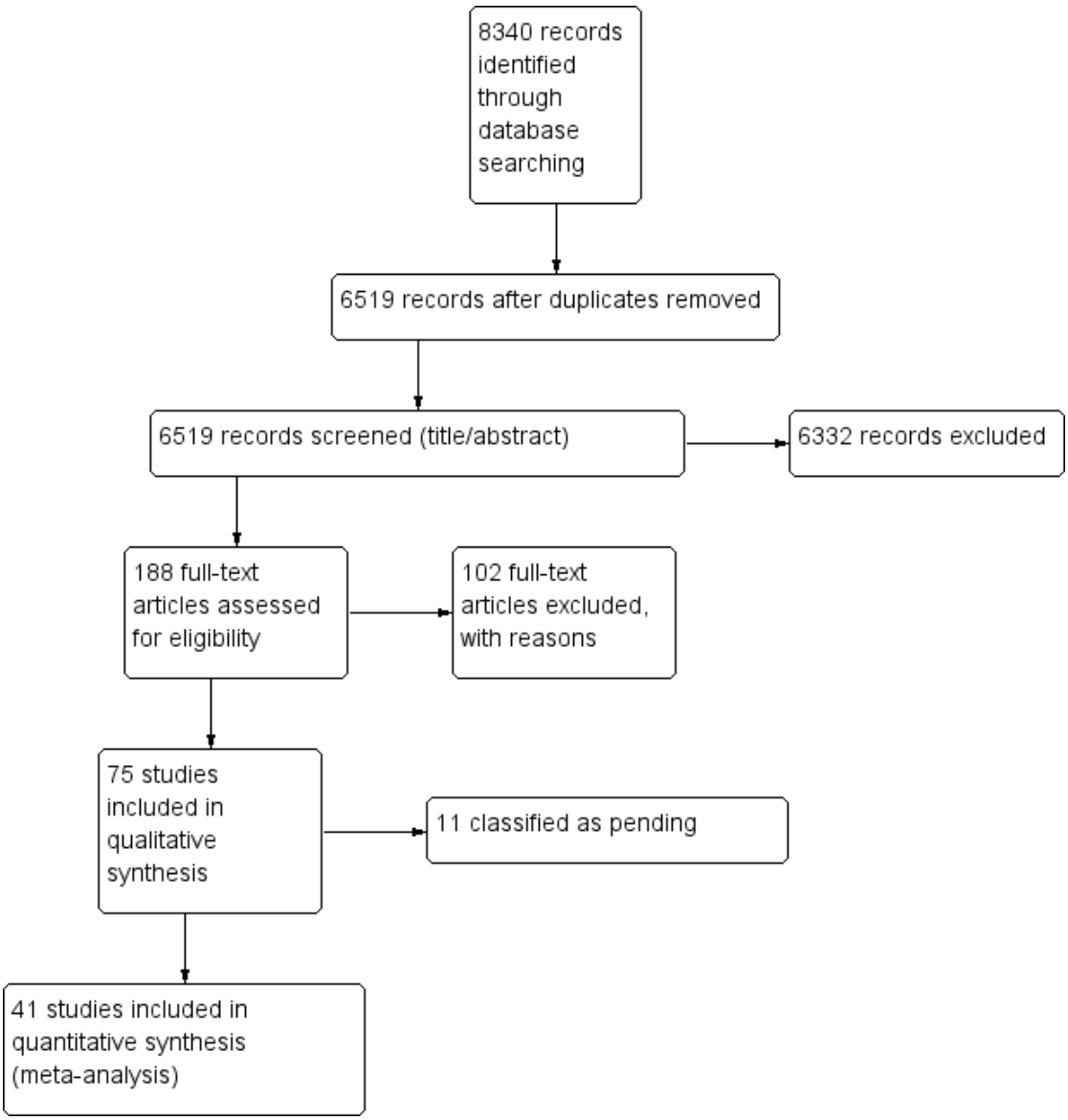
papers. Eleven papers are in Studies awaiting classification, as some data are not presented in the papers and the trial authors should be contacted for important details allowing definitive inclusion or exclusion of the studies (Figure 1).

Figure 1. Study flow diagram.



For this update, we ran the searches in November 2011 and found 4223 records (after duplicates were removed). After screening of title and abstracts, we retrieved 36 citations in full-text for evaluation. We excluded ten (see Characteristics of excluded studies), classified 11 as pending, and included 15.

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Included studies

We have coded each trial on the basis of study design and type of data contributed to the review as follows.

The letters coming before the study represent study design: a denotes RCTs, b denotes case-control studies and c denotes cohort studies. The second letter indicates the contribution to the evidence in the efficacy/effectiveness data set (letter a) or harms (letter b). So, for example, a case-control study contributing safety or harms data is coded as bb and a trial contributing efficacy/effectiveness data is coded as aa.

This review consists of 40 RCTs/CCTs (47 datasets), 12 case-controls (16 datasets), and 21 cohort studies (25 datasets). The 2011 update produced the inclusion of three RCTs (four datasets), nine case-controls (13 datasets), and three cohort studies (three datasets). Eight included trials (ab Desheva 2002; ab Grigor'eva 1994; aa Grigor'eva 2002; ab Rudenko 1991; aa Rudenko 1996b; ab Slepushkin 1974; ab Slepushkin 1991; ab Vasil'eva 1988a), eight included cohort studies (ca Burtseva 1991; ca Chumakov 1987; ca El'shina 2000; aa Rudenko 1988; cb Slepushkin 1994; ca Slobodniuk 2002a; ca Vasil'eva 1982; ab Vasil'eva 1988b), and a CCT (ab Aksenov 1971) were translated from Russian. We sent six requests to trial authors for further data (split by age), and two trial authors provided the data requested.

Included studies are classified below on the basis of the evidence provided. We included studies listed under 'Effectiveness and safety' and 'Effectiveness only' in our quantitative analysis. We included studies listed under 'Effectiveness and safety' and 'Safety only' in our qualitative analysis of vaccine safety only (see Adverse Events paragraph).

Effectiveness and safety

- **RCTs** (15 studies/21 datasets): **RCT-cluster randomisation**:aa Alexandrova 1986; aa Clover 1991; aa Gruber 1990; aa Rudenko 1993a; aa Rudenko 1993b; aa Rudenko 1996a; aa Rudenko 1996b. **RCT-individual randomisation**: aa Belshe 1998; aa Belshe 2000a; aa Beutner 1979a; aa Beutner 1979b; aa Bracco Neto 2009a; aa Bracco Neto 2009b; aa Colombo 2001; aa Grigor'eva 2002; aa Khan 1996; aa Rudenko 1988; aa Tam 2007a; aa Tam 2007b; aa Vesikari 2006a; aa Vesikari 2006b.
- **Prospective cohort** (5 studies/5 datasets): ca Burtseva 1991; ca El'shina 2000; ca Kawai 2003; ca King 2006; ca Vasil'eva 1982.

Effectiveness only

- **RCT** (2 studies/3 datasets): aa Hoberman 2003a; aa Hoberman 2003b; aa Principi 2003.
- **Prospective cohort** (9 studies/11 datasets): ca Chumakov 1987; ca Fujieda 2006; ca Jianping 1999; ca Maeda 2002; ca Maeda 2004a; ca Maeda 2004b; ca Maeda 2004c; ca Ozgur 2006; ca Salleras 2006; ca Wiggs-Stayner 2006; ca Yin 2011.
- **Pandemic prospective cohort** (1 study/1 dataset): ca Ortqvist 2011.
- **Retrospective cohort** (2 studies/4 datasets): ca Allison 2006; ca Slobodniuk 2002a; ca Slobodniuk 2002b; ca Slobodniuk 2002c.
- **Case-contro**l (7studies/11 datasets): ba Anonymous 2005; ba Cochran 2010a; ba Cochran 2010b; ba Cochran 2010c; ba Eisenberg 2008a; ba Eisenberg 2008b; ba Hirota 1992; ba Kelly 2011; ba Kissling 2011; ba Staat 2011a; ba Staat 2011b.
- **Pandemic case-control** (4 studies/4 datasets): ba Gilca 2011; ba Mahmud 2011; ba Valenciano 2011; ba Van Buynder 2010.

Safety only

- **RCT** (21 studies/21 datasets): ab Belshe 1992; ab Desheva 2002; ab Grigor'eva 1994; ab Gruber 1996; ab Gruber 1997; ab Gutman 1977; ab King 1998; ab Levine 1977; ab Mallory 2010; ab Obrosova-Serova 1990; ab Plennevaux 2011; ab Rudenko 1991; ab Slepushkin 1988; ab Slepushkin 1991; ab Steinhoff 1990; ab Steinhoff 1991; ab Swierkosz 1994; ab Vasil'eva 1988a; ab Vasil'eva 1988b; ab Wright 1976a; ab Zangwill 2001.
- **Prospective cohort** (1 study/1 dataset): cb Slepushkin 1994.
- **Pandemic prospective cohort** (1 study/1 dataset): cb MPA 2011.
- **Case-control** (1 study/1 dataset): bb Goodman 2006.

Interepidemic studies:

- **RCT** (1 study/1 dataset): ab Slepushkin 1974. **CCT** (1 study/1 dataset): ab Aksenov 1971.
- **Retrospective cohort** (2 studies/2 datasets): cb Nicholls 2004; cb Ritzwoller 2005.

For this 2011 update we included the following studies and datasets in the review: aa Bracco Neto 2009a; aa Bracco Neto 2009b; ba Cochran 2010a; ba Cochran 2010b; ba Cochran 2010c; ba Eisenberg 2008a; ba Eisenberg 2008b; ba Gilca 2011; ba Kelly 2011; ba Kissling 2011; ba Mahmud 2011; ab Mallory 2010; cb MPA 2011; ca Ortqvist 2011; ab Plennevaux 2011; ba Staat 2011a; ba Staat 2011b; ba Valenciano 2011; ba Van Buynder 2010; ca Yin 2011. Readers are reminded that one study may provide multiple datasets (i.e. aa Bracco Neto 2009a; aa Bracco Neto 2009b).

Excluded studies

We excluded 102 studies mainly because they were non-comparative, or because they had not been carried out in healthy children, or because they assessed the impact of vaccinating children to prevent influenza in the elderly, or because they presented only

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serological outcome or data published in studies already included in this review (See Characteristics of excluded studies tables).

Risk of bias in included studies

RCTs/CCTs

We included seventeen trials (corresponding to 24 datasets) in the vaccine efficacy or effectiveness analyses.

We classified five RCTs (eight datasets) as having low risk of bias aa Alexandrova 1986; aa Belshe 1998; (aa Beutner 1979a - aa Beutner 1979b); (aa Hoberman 2003a - aa Hoberman 2003b); (aa Tam 2007a - aa Tam 2007b). Two RCTs reported data from two influenza seasons. In both cases we classified the first season at low risk of bias (two datasets): aa Bracco Neto 2009a; aa Vesikari 2006a; whereas we classified the second one for both studies (two datasets) as high risk of bias: aa Bracco Neto 2009b; aa Vesikari 2006b. Five RCTs (five datasets) presented an unclear risk of bias for one or more key domains, then a plausible bias that raises some doubt about the results: aa Clover 1991; aa Grigor'eva 2002; aa Gruber 1990; aa Khan 1996; aa Principi 2003. Finally we considered five RCTs (seven datasets) to have high risk of bias: aa Belshe 2000a; aa Colombo 2001; aa Rudenko 1988; (aa Rudenko 1993a - aa Rudenko 1993b); (aa Rudenko 1996a - aa Rudenko 1996b). Overall, out of 24 datasets providing evidence of efficacy and effectiveness, 42% (10/24) were at low risk of bias, 21% (5/24) had unclear risk of bias, and 37% (9/24) were at high risk of bias (Figure 2).

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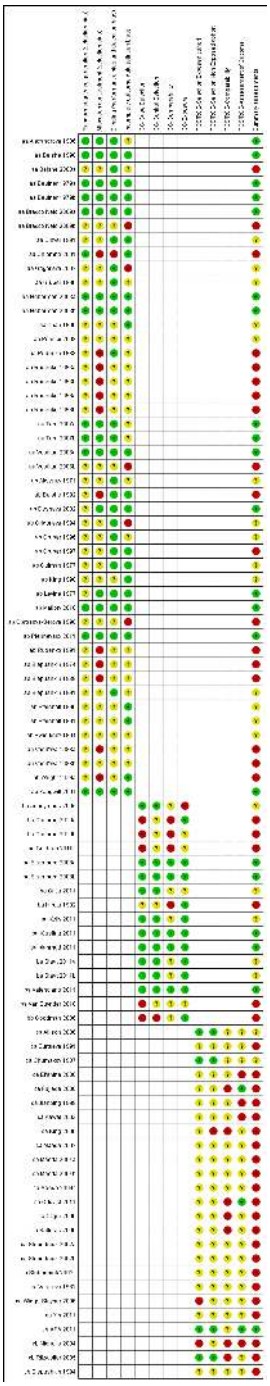
Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



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We included 23 RCTs/CCTs (corresponding to 23 datasets) reporting vaccine safety outcome only.

We classified five RCTs at low risk of bias: ab Desheva 2002; ab Levine 1977; ab Mallory 2010; ab Plennevaux 2011; ab Zangwill 2001. Nine RCTs (corresponding to nine datasets) had an unclear risk of bias: ab Aksenov 1971; ab Grigor'eva 1994; ab Gruber 1996; ab Gutman 1977; ab King 1998; ab Slepushkin 1991; ab Steinhoff 1990; ab Steinhoff 1991; ab Swierkosz 1994. Finally, we classified nine RCTs (nine datasets) at high risk of bias: ab Belshe 1992; ab Gruber 1997; ab Obrosova-Serova 1990; ab Rudenko 1991; ab Slepushkin 1974; ab Slepushkin 1988; ab Vasil'eva 1988a; ab Vasil'eva 1988b; ab Wright 1976a.

Overall, out of 23 datasets providing evidence of vaccine safety only, 22% (5/23) were at low risk of bias, 39% (9/23) had an unclear risk of bias, and 39% (9/23) were at high risk of bias (Figure 2).

Case-control studies

We included 11 case-control studies (corresponding to 15 datasets) in vaccine efficacy analyses.

Four studies (5 datasets) were at low risk of bias: (ba Eisenberg 2008a-ba Eisenberg 2008b); ba Kissling 2011; ba Mahmud 2011; ba Valenciano 2011. Four studies (5 datasets) had an unclear risk of bias for one or more key domains: ba Kelly 2011; (ba Staat 2011a; ba Staat 2011b); ba Anonymous 2005; ba Gilca 2011. Three studies (five datasets) were at high risk of bias: (ba Cochran 2010a; ba Cochran 2010b; ba Cochran 2010c); ba Hirota 1992; ba Van Buynder 2010.

Overall, out of 15 datasets providing evidence of vaccine efficacy, 33.3% (5/15) were at low risk of bias, 33.3% (5/15) had an unclear risk of bias and 33.3% (5/15) were at high risk of bias (Figure 2).

We classified the only case-control study with a safety outcome, bb Goodman 2006, at high risk of bias.

Cohort studies

We included 17 cohort studies (corresponding to 21 datasets) in vaccine efficacy or effectiveness analyses.

Two studies (two datasets) had an unclear risk of bias: ca Allison 2006; ca Chumakov 1987. Fourteen studies (19 datasets) were at high risk of bias: ca Burtseva 1991; ca El'shina 2000; ca Fujieda 2006; ca Jianping 1999; ca Kawai 2003; ca King 2006; ca Maeda 2002; ca Maeda 2004a; ca Maeda 2004b; ca Maeda 2004c; ca Ortqvist 2011; ca Ozgur 2006; ca Salleras 2006; ca Slobodniuk 2002a; ca Slobodniuk 2002b; ca Slobodniuk 2002c; ca Vasil'eva 1982; ca Wiggs-Stayner 2006; ca Yin 2011.

Overall, out of 21 datasets, 9.5% (2/21) had unclear risk of bias and 90.5% (19/21) were at high risk of bias (Figure 2).

Of the four cohort studies (corresponding to four datasets) included in vaccine safety only: only one (one dataset) was at low risk of bias (cb MPA 2011) and three studies (three datasets) were at high risk of bias: cb Nicholls 2004; cb Ritzwoller 2005; cb Slepushkin 1994.

Allocation

Of the 17 included RCTs (24 datasets), adequate allocation concealment is reported in seven studies (10 datasets). We assessed allocation concealment as satisfactory only in the first season of the two-season trials by aa Belshe 1998; aa Bracco Neto 2009a; aa Vesikari 2006a.

Blinding

In the included studies blinding was performed well in 27 datasets out of 47 (57%). Nineteen datasets showed unclear blinding and one was not blinded.

Incomplete outcome data

Few studies reported information on influenza circulation in the surrounding community, making interpretation of the results and assessment of their generalisability difficult.

Selective reporting

There is evidence of sizeable reporting bias of all types in influenza vaccines studies in general (Jefferson 2009), in the publication of 2009 H1N1 pandemic vaccines studies (Ioannidis 2011) and in the harms in children (Jefferson 2005a).

Other potential sources of bias

Twenty-five studies reported that written consent had been obtained from the parents of study participants (ab Belshe 1992; aa Belshe 1998; aa Belshe 2000a; aa Beutner 1979a; aa Clover 1991; aa Colombo 2001; aa Gruber 1990; ab Gruber 1996; ab Gruber 1997; ab Gutman 1977; ba Hirota 1992; aa Hoberman 2003a; ca Kawai 2003; aa Khan 1996; ab King 1998; ab Levine 1977; ca Maeda 2002; ca Maeda 2004a; aa Rudenko 1993a; aa Rudenko 1996a; ab Slepushkin 1988; ab Steinhoff 1990; ab Steinhoff 1991; ab Swierkosz 1994; ab Wright 1976a), another two refer to parental permission being granted (ab Desheva 2002; ca El'shina 2000), and one study refers to voluntary participation (cb Slepushkin 1994). Seven studies reported that the trial had received approval from a local review body (aa Beutner 1979a; aa Clover 1991; aa Gruber 1990; aa Hoberman 2003a; aa Rudenko 1993a; ab Slepushkin 1991; cb Slepushkin 1994).

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The main problem we encountered in interpreting studies included in the 2007 update was that of high risk of bias: all included studies were poorly reported and contained either contradictions between data in figures, tables and text, or reported implausible events or showed evidence of reporting bias of one sort or another. The two placebo-controlled trials of cold adapted influenza vaccine (CAIV) reported safety data in a partial fashion with data missing for up to a third of participants. The reporting format of both trials (which had the same sponsors) was similar and so were the inconsistencies, which suggests either a pre-set format from the same sponsor or the presence of one or more ghost authors, or both.

We encountered similar problems in the 2011 update, especially in cohort studies and a specific type of case-control study.

Effects of interventions

Quantitative data synthesis

We constructed the following eight comparisons for our meta-analysis.

- Four comparisons included evidence from RCTs: **comparison 01** (Analysis 1.1, Analysis 1.2); **comparison 02** (Analysis 2.1, Analysis 2.2); **comparison 05** (Analysis 5.1, Analysis 5.2, Analysis 5.3, Analysis 5.4, Analysis 5.5, Analysis 5.6); and **comparison 06** (Analysis 6.1, Analysis 6.2).
- One comparison included case-control studies: **comparison 07** (Analysis 7.1, Analysis 7.2, Analysis 7.3).
- Two comparisons included evidence from cohort studies: **comparison 03** (Analysis 3.1, Analysis 3.2) and **comparison 04** (Analysis 4.1, Analysis 4.2, Analysis 4.3).
- One comparison was constructed for the all-outcomes for all-vaccine types versus placebo: **comparison 08** (Analysis 8.1, Analysis 8.2, Analysis 8.3, Analysis 8.4, Analysis 8.5, Analysis 8.6, Analysis 8.7, Analysis 8.8, Analysis 8.9, Analysis 8.10, Analysis 8.11).

Comparison 01 and **comparison 05** included evidence from live attenuated vaccines, whereas **comparison 02** and **comparison 06** included evidence from inactivated vaccines. All comparators were placebo or do-nothing and **comparisons 01, 02, 03** and **04** were stratified by available age groups, i.e. under two years; under six years, and over six years of age, and by type of outcome.

The comparisons with influenza as an outcome (Analysis 1.1 and Analysis 3.1 for live vaccines; Analysis 2.1 and Analysis 4.1 for inactivated vaccines) therefore summarise the evidence of vaccine efficacy. The comparisons with ILI as an outcome (Analysis 1.2 and Analysis 3.2 for live vaccines; Analysis 2.2 and Analysis 4.2 for inactivated vaccines) summarise vaccine effectiveness.

Comparison 08 (Analysis 8.3 to Analysis 8.8) (for placebo-controlled trials) included data for rare outcomes (secondary cases, school absences, lower respiratory tract disease, acute otitis media and its consequences and socioeconomic impact). Due to scarcity of data (most outcomes were reported by one or two studies only) no age stratification was possible for these outcomes.

Comparisons showing vaccines' efficacy

Comparison 01 (Analysis 1.1, evidence from RCTs) shows that live attenuated vaccines have 80% overall efficacy (RR 0.20; 95% CI 0.13 to 0.32). The RD for children under the age of 6 is -0.15 (95% CI -0.20 to -0.10); NNV = 7, but we could find no usable age-specific data for those aged two or less. One study on 1632 children aged 15 to 71 months (aa Belshe 1998) did report differences in incidence of influenza in one-year-olds of 17% and 86% and for two-year-olds of 24% and 96% for placebo and vaccination arms, respectively. These figures are presented in the Discussion section of the paper, but in the absence of an age breakdown, we could not include these data in the meta-analysis.

The overall RD for those aged 2 to 16 years is -0.16 (95% CI -0.20 to -0.11); NNV = 6. At least six children over the age of two must be vaccinated to avoid one case of influenza (i.e. one set of symptoms with one infection).

For inactivated vaccines, comparison 02 (Analysis 2.1, evidence from RCTs) shows lower efficacy (VE = 59%) (RR 0.41; 95% CI 0.29 to 0.59) than live attenuated vaccines. In children aged two or less the vaccines (are not significantly more efficacious than placebo) may reduce the risk by almost half (RR 0.55; 95% CI 0.18 to 1.69), but as this observation is based on a single, relatively small study (aa Hoberman 2003a) the estimate is imprecise and the 95% CI is wide. The RD for those aged six or older is -0.35 (95% CI -0.54 to -0.15); NNV = 3. The NNV calculated using the RR (0.29; 95% CI 0.21 to 0.41) would be 4.

Comparison 03 (Analysis 3.1, evidence from cohort studies) shows that live attenuated vaccines have 44% VE (RR 0.56; 95% CI 0.35 to 0.91) although this observation is based on a single, small study in children aged over six years (ca Burtseva 1991).

Comparison 04 (Analysis 4.1, evidence from cohort studies) shows that inactivated vaccines have 64% VE (RR 0.36; 95% CI 0.12 to 1.11) in the over six years age group, 66% VE (RR 0.34; 95% CI 0.13 to 0.89) in children up to six years of age, and are no better than placebo in children aged below two years (RR 0.63; 95% CI 0.27 to 1.47).

Comparisons showing vaccines' effectiveness

Comparison 01 (Analysis 1.2, evidence from RCTs) shows that live attenuated vaccines have 33% overall effectiveness (RR 0.67; 95% CI 0.62 to 0.72), but we could find no evidence for children aged two years or below. The RD for all age groups except two years and below is -0.08, (95% CI -0.11 to -0.06); NNV = 12.

Comparison 02 (Analysis 2.2, evidence from RCTs) shows that inactivated vaccines have 36% overall effectiveness (RR 0.64; 95% CI 0.54 to 0.76). We could find no evidence for children aged two

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years or below. The RD for all age groups except two years and below is -0.12 (95% CI -0.16 to -0.08); NNV = 8.

Comparison 03 (Analysis 3.2, evidence from cohort studies) shows that live attenuated vaccines are 37% effective in the over five age group (RR 0.63; 95% CI 0.57 to 0.69).

Comparison 04 (Analysis 4.2, evidence from cohort studies) shows that inactivated vaccines have overall 47% effectiveness (RR 0.53; 95% CI 0.42 to 0.67). Data from a very small single study (ca Yin 2011) report an effectiveness of 53% in children under the age of two. Effectiveness in children aged up to six years (RR 0.74; 95% CI 0.59 to 0.93) is just statistically significant. However, this must be interpreted with caution because the sizeable decrease in RR since the 2005 version of our review is due to the inclusion of a large cohort study at high risk of bias (ca Fujieda 2006). Inactivated vaccines were more effective (VE = 56%) (RR 0.44; 95% CI 0.29 to 0.68), in children aged six years or more.

In the case-control study testing the effectiveness against ILI of an inactivated vaccine during an outbreak in 803 children aged 6 to 12 years (ba Hirota 1992) (comparison 07, Analysis 7.3), the vaccine was well matched antigenically to the circulating strain. Its administration was inversely associated with risk of severe ILI but not with mild ILI (no ORs are reported).

The case-control study testing the effect against laboratory-confirmed influenza of inactivated influenza vaccine in children aged below six years showed OR 0.59 (95% CI 0.45 to 0.77) 41% VE, 95% CI (23% to 55%) in comparison 07 (Analysis 7.1) performed with crude data.

In comparison 07 (Analysis 7.2) performed with adjusted estimates, the OR in children below 23 months was 0.60 (95% CI 0.39 to 0.94), 40% VE; in children between 24 and 59 months (OR 0.40; 95% CI 0.22 to 0.70), 60% VE; in children 6 to 59 months (OR 0.45; 95% CI 0.32 to 0.62), 55% VE; and in children below 14 years (OR 0.23; 95% CI 0.06 to 0.84), 77% VE.

Evidence on rarer outcomes

Comparison 08 (Analysis 8.3 to Analysis 8.11) assessed evidence from RCTs on rare outcomes. Vaccines were significantly more effective either than placebo in reducing school absence (RR 0.49; 95% CI 0.26 to 0.92) or than standard care (RR 0.14; 95% CI 0.07 to 0.27). Both observations are based on single studies (aa Colombo 2001; aa Khan 1996). However, the RD is non-significant. A third trial found a significant reduction in school days missed by vaccinated children (mean difference (MD) -4.23; 95% CI -6.81 to -1.65); aa Principi 2003). A trial showed a significant effect of CAIV-T against outpatients attendance for pneumonia and influenza (OR 0.60; 95% CI 0.43 to 0.82) and parents' working days lost (OR 0.62; 95% CI 0.39 to 1.00) (aa Vesikari 2006a). The effects on all other outcomes (secondary cases, lower respiratory tract disease, drug prescriptions, acute otitis media and its consequences and socioeconomic impact) were not significantly different from those of placebo or standard care. According to one possible cohort study at high risk of bias (ca Ozgur 2006), inactivated vaccines do not reduce the risk of acute otitis media (although this may be due to the small denominator of 119). Virosomal vaccines (engineered to resemble the antigenic structure of the influenza virus) reduce antibiotic consumption (OR 0.77; 95% CI 0.61 to 0.98), school absenteeism (OR 0.42; 95% CI 0.34 to 0.51), and work absenteeism (OR 0.69; 95% CI 0.51 to 0.93). These observations must be interpreted with caution as they are based on a single cohort study at high risk of bias (ca Salleras 2006).

For completeness we have summarised available evidence of efficacy and effectiveness from intraepidemic and non-typical studies in Table 3.

Evidence on number of doses

Comparison 08 (Analysis 8.1) between the efficacy of one- and two-dose schedules of live attenuated vaccines versus placebo appear to favour the two-dose schedule: 73% efficacy (RR 0.27; 95% CI 0.12 to 0.61) (aa Belshe 1998; aa Belshe 2000a; aa Clover 1991; aa Gruber 1990) compared with 89% efficacy (RR 0.11; 95% CI 0.04 to 0.26), although this estimate is based on two two-dose studies only (aa Belshe 1998; aa Vesikari 2006a). All inactivated vaccine trials were conducted using a one-dose schedule. The one-dose virosomal vaccine was both efficacious and effective in children aged 3 to 14 years (RR 0.11; 95% CI 0.03 to 0.49) and (RR 0.26; 95% CI 0.17 to 0.60). However, these observations must be interpreted with caution as they are based on a single cohort study at high risk of bias (ca Salleras 2006).

Sensitivity analysis

Pooling all age data made no difference to our conclusions. Exclusion of evidence from Russian studies had the effect of making some of the comparisons not significant and depopulating single-study comparisons, but did not materially affect our conclusions. However, we have no reason to believe that vaccines produced in the former USSR have different performance from their Western counterparts. The only study directly comparing the effectiveness of trivalent inactivated split-virus vaccine (Wyeth-Ayerst) with trivalent live attenuated, cold adapted influenza vaccine (Odessa production company, Ukraine) with placebo on school absences failed to show any significant difference in performance (aa Khan 1996).

Table 1 shows the results of the stepwise sensitivity analysis excluding Russian/USSR studies. All comparisons except Analysis 1.1 and Analysis 1.2 (influenza and ILI in live vaccine trials) were sensitive to the exclusion of evidence from Russian/USSR studies. For comparison Analysis 1.2 exclusion of seven independent data sets made the effectiveness estimate non-significant in children older than six years but enhanced the total effectiveness from 33% to 88%. For comparison Analysis 2.2, effectiveness estimates for

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children older than six years were not significantly affected but were increased from 28% to 76%. Comparisons Analysis 3.1 and Analysis 3.2 were depopulated by the removal of the one dataset in each group. For comparison Analysis 4.1, the non-significant 64% estimate for children older than six years became significant (80%), whereas for comparison Analysis 4.2, the estimates for those older than six years (56%) remained significant but increased in size.

Table 2 reports the results of the sensitivity analysis performed excluding studies (datasets) with high risk of bias. The results of Analysis 1.1 and Analysis 1.2 were sensitive to exclusion of the high risk of bias datasets. However, these do not alter results on vaccine efficacy or effectiveness described in the review. Analysis 2.1 does not include evidence from studies with high risk of bias and its results are unchanged. Analysis 2.2 is sensitive to exclusion of evidence from high risk of bias studies. Specifically, evidence of effectiveness in children under six years becomes not statistically significant with a VE reduction from 61% to 48%. In children over six years of age, exclusion of high risk of bias datasets produced an increase of VE from 28% to 76% and overall VE increased form 36% to 61%. Analysis 3.1, Analysis 3.2, Analysis 4.1 and Analysis 4.2 are depopulated because data for this comparison came from high risk of bias studies only. Evidence from Analysis 5.1 to Analysis 7.2 are sensitive to exclusion of high risk of bias studies, but this does not alter conclusions. Evidence from Analysis 7.3 disappears. Evidence from Analysis 8.1 to Analysis 8.11 are sensitive to exclusion of high risk of bias studies but this does not alter the conclusions of the review.

Safety studies

Adverse events

In previous versions of the review we provided extensive documentation of the loss of evidence due to differing definitions and reporting formats of harms, chiefly local adverse events. For simplicity and to ease reading, we have deleted the tables.

Randomised controlled trials

Twenty-nine studies presented data on the safety of live influenza vaccines in children aged 2 months to 17 years old (Alexandrova 1986; Belshe 1992; Belshe 1998; Belshe 2000a; Beutner 1979a; aa Bracco Neto 2009a; Desheva 2002; Grigor'eva 1994; Grigor'eva 2002; Gruber 1990; Gruber 1996; Gruber 1997; Khan 1996; King 1998; ab Mallory 2010; Obrosova-Serova 1990; Piedra 2002a; Rudenko 1988; Rudenko 1991; Rudenko 1993a; Rudenko 1996a; Slepushkin 1991; Slepushkin 1994; Steinhoff 1990; Swierkosz 1994; Tam 2007; Vesikari 2006a; Vesikari 2006b; Zangwill 2001).

Eight studies presented safety data for inactivated vaccines in children aged 6 months to 18 years old (Gruber 1990; Gutman 1977; Khan 1996; Levine 1977; ab Plennevaux 2011; Slepushkin 1991; Vasil'eva 1988a; Wright 1976a) and one paper, El'shina 2000, contained an RCT of short-term safety data (≤ five days) and a cohort study of long-term safety data (≤ five months).

Temperature rise as an outcome was presented in most of the RCTs, with large differences among trials. Considering only studies reporting raw data on this outcome, the proportion of vaccinated children with fever ranged from 0.16% (Rudenko 1993a) to 15% (Belshe 1998), while in the placebo groups this proportion ranged from 0.71% (Rudenko 1993a) to 22% (Gruber 1996).

Three studies reported raw data for nasal congestion (Belshe 1998; Belshe 2000a; Gruber 1996). Studies conducted by Belshe assessed safety of cold-adapted trivalent influenza vaccine, while the study by Gruber et al assessed live attenuated vaccine. The proportion of vaccinated children with nasal congestion ranged from 19% (Belshe 2000a) to 78% (Gruber 1996), while in the control group this proportion ranged from 14% (Belshe 2000a to 68% (Gruber 1996).

Data on upper respiratory tract infections were reported by Belshe 1992: in the vaccinated arms the proportion of children affected ranged from 53% to 70%, while in the placebo group this outcome was found in 47% of children.

aa Bracco Neto 2009a and aa Bracco Neto 2009b (one study run over two seasons) reported a significant difference in the rate of bronchitis between live attenuated influenza vaccine (LAIV) and saline placebo recipients (3.1% and 1.6% respectively; P = 0.046), while the incidence of bronchospasm was also similar between groups (1.8% and 1.5% respectively).

ab Mallory 2010 reported headache as the most common solicited symptom in children receiving H1N1 LAIV through day 8 after dose one which was reported by 16.6% and 15.4% of H1N1 LAIV and placebo recipients respectively, rate difference 1.2% (95% CI -10.2% to 10.2).

Three RCTs included data on reactions to live vaccine within six weeks of inoculation (short-term outcomes). Belshe 1998 included serious adverse events up to 42 days after vaccination. From the same trial, Piedra 2002a (see aa Belshe 1998) included the following outcomes between 11 and 42 days after vaccination: afebrile illness, analgesic/antipyretic use, antihistamine/decongestant/antitussive use, febrile illness, febrile otitis media, lower respiratory tract infection, oral antibiotics use and otitis media. In the (ab Plennevaux 2011) study, within 21 days since the last of the two injections a range from 42% to 55% of participants in each age and vaccine group experienced unsolicited adverse events, considered by the investigator, in most cases, not to be vaccine related. ab Mallory 2010 reported adverse events during days 1 to 15 after doses one and two. Adverse events after dose one were reported in 18.1% and 16.9% of H1N1 LAIV and placebo recipients respectively, and in 13.7% and 14.3% of recipients after dose two. The most common adverse events in children after dose one were nausea (1.9% versus 3.1%), vomiting (2.7% versus 1.5%) and diarrhoea (1.5% versus 1.5%).

For longer-term outcomes, Belshe 1998 included vaccine related

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serious adverse events within 102 days of inoculation. Three RCTs included safety outcome followed up for six months after inoculation. Desheva 2002 included three outcomes: allergies, infections (excluding influenza and acute respiratory infections) and other somatic illnesses. Rudenko 1988 included only morbidity (excluding influenza and acute respiratory infections). Rudenko 1996a included 13 outcomes including allergies and five respiratory tract disease outcomes.

Seven RCTs reported data on short-term outcomes following inoculation with inactivated vaccines. In particular, two RCTs reported data on erythema, swelling and induration (Beutner 1979a; Wright 1976a), two other studies on pain/tenderness (Beutner 1979a; Gruber 1990), and one study reported data on infiltration and hyperemia (Vasil'eva 1988a).

Safety outcomes data up to six months after inoculation of inactivated vaccine were presented in one RCT (Vasil'eva 1988a) (15 outcomes).

Observational studies

Three cohort studies presented safety data for inactivated vaccines in children aged 12 months to 18 years old (Slepushkin 1994; Vasil'eva 1982; Vasil'eva 1988b) and one paper (El'shina 2000) contained a RCT of short-term safety data (≤ five days) and a cohort study of long-term safety data (≤ five months).

One cohort study (Slepushkin 1994) compared the reactogenicity and immunogenicity of live bivalent or trivalent vaccines and inactivated bivalent and trivalent vaccines in 1817 children in three cohorts between 1989 and 1991. Reactions to the vaccines were studied for five days after vaccination. A temperature of 37.5 °C was considered a weak reaction, and from 37.6 to 38.5 °C a severe reaction. When a trivalent vaccine was administered subcutaneously to children aged 11 to 14 years in 1990, temperature reactions were recorded in 2.6% of participants, moderate local reactions in 3.2%, and severe local reaction in 0.7%. Consequently, the intramuscular route was used for the 7 to 10 years group where a lower frequency of reactions was recorded. In 1991, the inactive vaccine caused moderate temperature reactions (37.6 °C to 38.5 °C) in 1.3% of the participants and moderate local reactions (26 to 50 mm hyperemia) in 4.4% of the participants.

Vasil'eva 1982 reported safety data of 335 children aged 7 to 15 years vaccinated with inactivated influenza vaccine. Participants were monitored for reactions by daily physical examination for five days following inoculation. Temperature, headache or malaise, sore throat and local reactions (hyperemia or cutaneous wheal) were the outcomes recorded. Mild fever (37.0 °C to 37.5 °C) was observed in 20% to 25% of children aged 7 to 10 years and 8% to 12% of children aged 11 to 15 years. Isolated cases of moderate and severe fever, above 37.6 °C were recorded in all groups. There were no statistical differences in systemic reactions between vaccine and placebo, between age groups or for method of administration. Local reactions were most frequent in children aged 11 to 15 years vaccinated with a syringe; 26.5% of participants from this subgroup showed moderate reactions (2.6 to 4.9 mm).

El'shina 2000 reported long-term safety data. The outcomes presented were cardiovascular illnesses, upper respiratory tract infection, Illnesses of stomach and intestines, skin diseases, allergies and infectious illnesses. There were no statistically significant differences between groups for the above safety outcomes. Incidences were rare and there was no difference between vaccinated and unvaccinated groups.

Vasil'eva 1988b assessed the safety of multiple immunisations of an inactivated bivalent influenza A vaccine in 12,643 children aged 11 to 14 years. All participants were followed up for 30 days after inoculation to determine the frequency of requests for urgent medical attention and of hospitalisation. The safety outcomes presented were increase in temperature, local reactions and intoxication/catarrh in the nasopharynx. The frequency of weak temperature reactions (< 37.5 °C) varied from 6.6% to 37.9% in vaccinated groups and 2.9% to 29.0% in placebo groups. Moderate temperature reactions occurred in isolated cases; the maximum frequency was 1.9% in children vaccinated four times who also showed the highest frequency of headaches and catarrh (11.1%). However, there were no statistically significant differences between vaccine and placebo groups. There was some increase in local reactions with an increase in number of inoculations (the percentage rising from 0.9% after one inoculation, 1.1% after three inoculations, and 1.9% after four inoculations), but these were not significantly different from responses in the placebo groups. No severe general or local reactions were observed in any child.

Serious adverse events

Safety data on serious adverse events were reported from three RCTs (aa Bracco Neto 2009a; ab Mallory 2010; ab Plennevaux 2011) and one case-control study (Goodman 2006).

aa Bracco Neto 2009a reported in the first year of the study one or more serious adverse events in 5.0% of LAIV-LAIV recipients, 3.8% of LAIV-placebo recipients, 3.4% of excipient placebo recipients, and 4.1% of saline placebo recipients. During the second year of the study 1.6% and 2.4% of LAIV and placebo recipients, respectively, reported one or more serious adverse event(s). Most of the events were respiratory. Twenty-nine participants experienced serious adverse events considered to be related to study product: the most frequent were pneumonia, bronchopneumonia, bronchiolitis and bronchitis. Three deaths were reported: one was the result of *Escherichia coli* (*E. coli)* septicaemia diagnosed 18 days after receipt of the second dose of LAIV in year one, and two deaths were accidental. None of these cases were judged to be related to the study product by the investigators.

ab Plennevaux 2011 reported a maximum rate of 8% severe unsolicited events. In particular, in the age group 6 to 35 months, the proportion of children, vaccinated with 7.5 µg HA and 15 µg HA vaccines, who experienced severe adverse events were 5% and

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6% respectively, while no event occurred in the placebo group.
ab Mallory 2010 reported three serious adverse events in children during the study: hospitalisation for depression and osteomyelitis in vaccine recipients, and cellulitis in a placebo recipient; all were considered by the investigators to be unrelated to the study vaccine. One new onset chronic disease, attention deficit hyperactivity disorder, was reported in a placebo recipient.
The case-control study assessing safety of trivalent influenza vaccine (TIV) in 6 to 23 months-old children included in the 2007 update (Goodman 2006) reported a series of outcomes identified either by physicians combing the exposed population for possible outcomes of interest and then clustering the diagnosis by international code disease (ICD) categories and then using Vaccine Safety Datalink (VSD) categories. This kind of data mining is not likely to clarify the safety profile of TIV.
The monovalent Pandemic influenza vaccine Pandemirix (GSK) appears associated with the onset of narcolepsy and cataplexy in children. Current evidence does not support either a country specific spread or a lot-related problem (cb MPA 2011; THL 2012).
Elsewere in the literature there are sparse reports of harms associated with particular brands of inactivated influenza vaccines. This is the case of the 2010 TIV by CSL Ltd used mainly in Australia. One child in every 110, aged below five, vaccinated with the CSL vaccine had a febrile seizure. Australia suspended its use. These episodes highlight the insufficient regulatory attention to potential harms from influenza vaccines in children, as the registration trials for the CSL vaccine had been carried out on 162 children aged up to three years (Collignon 2010).
This degree of scrutiny to identify all global cases of missed potential harms is beyond the resources of this review.

DISCUSSION

Summary of main results

Our review shows that live attenuated influenza vaccines (LAIVs) have good relative efficacy (up to 80%), but lower relative effectiveness (around 33%) in children aged more than two years. LAIVs may be effective in controlling a school outbreak, although this observation is based on an old, poorly reported Russian study (ab Slepushkin 1974). LAIVs are not licensed for use in children aged below two years.
Inactivated vaccines have a lower relative efficacy (59%) than live attenuated vaccines, and in children aged two or less, they appear to have similar effects to placebo. This observation is based on a single small study (aa Hoberman 2003a). Under the age of six, TIV does not provide significant protection against influenza (has no significant efficacy), whereas the NNV for LAIV is 7. Below two years of age there is no evidence of effect of either LAIV or TIV. Their relative effectiveness is around 36% for children aged more than two, but we could find no evidence for children aged two years or below. Our conclusions on inactivated vaccines are based on almost 20,000 observations from randomised studies.
The absolute efficacy of both types of vaccines is widely different with NNV = 7 for LAIV and NNV = 28 for inactivated vaccine, respectively.
Evidence from cohort studies (11,000 observations) yield higher estimates, suggesting that inactivated vaccines have higher (up to 64%) efficacy and effectiveness (56%) in the over six years age group; in children aged less than two, their efficacy is no better than that of a control arm, and there is evidence from a single study of 53% effectiveness. However, readers should bear in mind the very low quality of the cohort datasets.
The differences between efficacy and effectiveness of the vaccines are not surprising as influenza vaccines are specifically targeted at influenza viruses and are not meant to prevent other causes of influenza-like-illness (ILI).
We found little evidence for other outcomes. Vaccines were up to 86% effective in reducing school absence. However, this observation is based on two small studies with a combined denominator of 899 (aa Colombo 2001; aa Khan 1996) and a third trial showing a mean absence reduction of four days (aa Principi 2003). A high risk of bias trial shows a significant effect of CAIV-T against outpatients' attendance for pneumonia and influenza and parents' working days lost (aa Vesikari 2006a). Evidence for other outcomes (secondary cases, lower respiratory tract disease, drug prescriptions, acute otitis media and its consequences and socioeconomic impact) suggests no difference with placebo or standard care. However, these conclusions are based on single studies, lacking statistical power except for the case of the outcome, acute otitis media. Virosomal vaccines reduce antibiotic consumption, school and work absenteeism, but these observations are based on a single cohort study at high risk of bias (ca Salleras 2006).
Our review includes 18 papers of 17 studies translated from Russian.

Overall completeness and applicability of evidence

Our review has several potential limitations. We could not find sufficient data to allow us to draw firm conclusions on vaccination routes (intramuscular or intranasal) or one- or two-dose schedules in inactivated vaccines.
The small number of included studies in each comparison does not allow for a sufficiently powerful test to assess empirical evidence of publication bias. The only method to mitigate publication bias is to include published and (if retrievable) unpublished literature, regardless of language or country.
Our meta-analysis showed significant heterogeneity. This could be due to differences in between-study follow-up periods (the longer the follow-up period the more the potential for identification of cases with vaccine effectiveness dilution as viral circulation de-

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clines), differences in ILI case definitions (our sensitivity analysis failed to show significant differences in case definition specificity), differences in performance of different live vaccines (we have no reason to believe this is so), differences in case-finding and in study quality, and differences in viral circulation levels.

Included studies provided insufficient data to stratify for viral circulation or duration of follow-up, but we do not believe heterogeneity affected our conclusions as our estimates are unequivocal and all point to high vaccine efficacy and lower effectiveness.

Quality of the evidence

The general methodological quality of included studies was poor. We found that description of vaccine content was variable and no preservatives or excipients were reported. We could find no comment on the degree of matching between virus strains used in the studies, circulating strains, and composition of yearly WHO recommended vaccines. In healthy adults antigenic composition is an important predictor of vaccine efficacy, as our Cochrane Review of influenza vaccines has shown (Jefferson 2010). The relative paucity of head-to-head comparisons of vaccines hinders meaningful comments on their relative performance and points to an absolute requirement for more direct comparison trials. Our 2005 decision to include non-randomised evidence in the evaluation of efficacy/effectiveness has had the consequence of including a large number of studies of dubious quality. This can be best observed in cohort studies. The majority of these are at high risk of bias and in case-control studies. We found several case-control studies of similar design which claimed to be testing the effectiveness of inactivated influenza vaccines in a real world setting (for example ba Cochran 2010a; ba Eisenberg 2008a; ba Kissling 2011; ba Kelly 2011; ba Mahmud 2011; ba Staat 2011a; ba Valenciano 2011; ba Van Buynder 2010). Cases and controls were both selected on the basis of the presence of ILI symptoms. The discriminating variable between cases and controls was the positivity (for influenza) of a laboratory-tested throat specimen. Consequently this design does not test the effect of vaccine exposure on the onset of ILI. It tests the effect of the vaccines on microbiological specimens, of dubious public health significance. We are unsure as to the value of such studies, apart from generating "noise" but little reliable evidence. The design of these studies is not coherent with the study objectives.

Potential biases in the review process

We found a large data set showing variable quality evidence of vaccines' efficacy in children aged two years or more.

As we had already observed in our Cochrane Review of influenza vaccines in healthy adults (Jefferson 2010), there is marked difference between the efficacy and effectiveness of the vaccines due to the large proportion of ILI ('the flu') caused by agents other than influenza viruses. This is an important point in the decision to vaccinate whole populations. In addition, we found limited evidence that vaccines reduce the burden of school absences. Decision makers' attention to the vaccination of very young children is not supported by the evidence summarised in our review. Although there is a growing body of evidence showing the impact of influenza on hospitalisations and deaths of children, at present we could find no convincing evidence that vaccines can reduce mortality, hospital admissions, serious complications or community transmission of influenza.

We were surprised to find only one safety study of inactivated vaccine in children under two years carried out nearly 30 years ago in 35 children (ab Wright 1976a). The lack of safety data for inactive vaccines in younger children is particularly surprising given that the inactive vaccine is now recommended for healthy children six months and older in the USA and Canada (AAPCID 2004; Harper 2004; Orr 2004). In contrast, while the live vaccine is only licensed for children aged five and older in the USA, 10 studies were found in which its safety has been tested in younger children. However, the manufacturers' refusal to release all safety outcome data from trials carried out in young children, together with obvious reporting bias and inconsistencies in the primary studies does not bode well for a fair assessment of the safety of live attenuated vaccines.

We found a notable range and diversity of safety outcomes and definitions (or lack of) in the included studies leading to a loss of data. This clearly demonstrates the difficulty of attempting to meta-analyse safety data for a review when it has not been presented in a standardised format. The Brighton Collaboration set up to facilitate the development, evaluation and dissemination of high quality information about the safety of human vaccines has produced guidelines (https://brightoncollaboration.org/internet/en/index/definition˙guidelines.html) on the recording and presentation of temperature and induration. The results of this search and review clearly show the need for the existence of such guidelines and their adoption by researchers worldwide.

Agreements and disagreements with other studies or reviews

Recently, the effects of influenza vaccination in those aged 16 or younger have been the topic of a number of other reviews. On the basis of their methods and of the inclusion criteria adopted, we classified the reviews into the following broad categories.

1) A first group of reviews that consider only studies with polymerase chain reaction (PCR)-confirmed or culture-confirmed clinical cases as primary efficacy outcome (Ambrose 2012; Belshe 2010; Carter 2011; Osterholm 2012; Rhorer 2009). All are focused on live attenuated influenza vaccine (LAIV) administration but also include studies comparing LAIV with trivalent influenza vaccine (TIV).

Ambrose 2012 and Rhorer 2009 are based on the same evidence,

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including trials performed on populations aged between 6 months and 17 years. Rhorer 2009 includes one placebo-controlled trial more than Ambrose 2012. In Ambrose 2012 the analysis is limited to the paediatric age group for which the vaccine is licensed (24 months or more at immunisation). Out of the nine included RCTs, six were placebo-controlled (corresponding to nine data sets), whereas controls were immunised with TIV in the remaining three included trials (three data sets). Both reviews show a high relative efficacy of a two-dose LAIV course against similar viral strains (about 80%) and a significantly lower efficacy of TIV.

The review by Osterholm 2012 includes evidence on both adult and paediatric populations. Included designs are either placebo-controlled trials or case-controlled studies. Looking only at studies performed on paediatric populations, placebo-controlled RCTs are the same as those included in Rhorer 2009. A pooled meta-analysis has been carried out on the same data sets (apart from one study - aa Bracco Neto 2009a; aa Bracco Neto 2009b). Evidence from case-control studies is also discussed (against seasonal or H1N1 pandemic influenza), even if it is not included in the analysis. Relative efficacy estimates of LAIV against PCR- or culture-confirmed influenza in children aged six months to seven years was around 80%.

Carter 2011 reports results of studies on LAIV efficacy, reactogenicity and immunogenicity in children and adult populations. Evidence of the vaccines' efficacy in children (i.e. against influenza, as opposed to ILI) is the same as that included in Rhorer 2009 (with the exception of Forrest 2008). Even if a meta-analysis was not performed, only a descriptive review is presented. Estimates of LAIV efficacy in comparison with placebo or TIV are the same as before. In contrast to the other reviews (Osterholm 2012; Rhorer 2009) that included the study by Lum 2010, Carter 2011 assessed the effect of MMR co-administration, concluding that this did not affect LAIV efficacy. The review also considers evidence on local and systemic reactions observed a few days after LAIV immunisation: runny nose, headache and tiredness are likely to occur more frequently among LAIV than among placebo recipients, especially after the first dose. LAIV is more reactogenic than TIV and its administration is associated with an increased risk of wheezing within 42 days after vaccination in children younger than five years of age in comparison with TIV.

2) A second group of systematic reviews (Manzoli 2007; Negri 2005) present several methodological analogies with our 2005 Cochrane review: the exceptions are that only RCTs or CCTs are included, safety issues of the vaccines are not considered and some included studies also had a vaccine control arm. The most recent one confirms that there are no significant differences between TIV and LAIV effects considering the three assessed outcomes (influenza, ILI, and otitis media). A sensitivity analysis was performed excluding Russian studies (classified at a lower level of methodological quality) from a pooled analysis and this resulted in a higher estimate of effect against clinical disease (pooled estimates for LAIV and TIV). Rodrigo Pendas 2007 includes studies (seven RCTs) evaluating the efficacy of both LAIV and TIV in preventing ILI, confirmed influenza, otitis media and other respiratory illnesses.

3) There is only one review presenting the effect of vaccination on the contacts of children (Jordan 2006). Results from the industry-funded review by Jordan 2006 including eight RCTs, three community studies and three economic evaluations are discussed, but a meta-analysis was not performed. The authors conclude that child vaccination could produce significant health benefits and be cost-saving to the community as a whole.

4) Two other reviews (Manzoli 2011; Yin 2011) evaluated the immunogenicity of monovalent H1N1 pandemic influenza vaccines (in both adjuvanted and non-adjuvanted formulations). All tested split/subunit vaccines induced a satisfactory immunogenicity (over 70%) after only one dose in adolescents, while only non-adjuvanted vaccines at high-doses and oil-in-water adjuvanted vaccines showed acceptable results for children. Even if the rate of serious adverse events was low for all 2009 H1N1 vaccines (0.013% overall) the review does not allow a firm conclusion to be drawn for vaccine safety at the population level. Mild to moderate adverse reactions were more frequent for oil-in-water adjuvanted vaccines. Wijnans 2011 reviews several studies (clinical trials, case reports, results of surveillance) reporting safety data of monovalent H1N1 pandemic vaccine.

The key question of the relationship between a surrogate outcome (antibody production) and field outcomes (clinical illness) is left unaddressed, calling into question the rationale for applying results from the reviews in deciding vaccination policies.

5) One other review (Michiels 2011) is based on evidence available in *The Cochrane Library* only (11 Cochrane Reviews; one other review/meta-analysis; 14 RCTs; 3 CCTs). The review provides a critical approach to the opportunity to administer inactivated influenza vaccine to children, adults and the elderly but also to individuals affected by comorbidity conditions (diabetes, chronic lung disease, cardiovascular disease, kidney or liver disease and immune suppression). Inactivated influenza vaccines appear to be effective in healthy adults and children over six years but not in children younger than two years and institutionalised elderly. Inconsistent results are found in studies in children younger than six years, individuals with chronic obstructive airways disease, institutionalised elderly, elderly with comorbidities, and healthcare workers in elderly homes. Vaccination of children might be protective in non-recipients of all ages living in the same community. The vaccination of pregnant women might be beneficial for their newborns.

Despite the great variety of method variations, the reviews all have similar conclusions to those of our 2005 Cochrane Review: TIV has few effects and there is no evidence that it affects deaths, complications or transmission of influenza. LAIV performed a little better at the expense of safety.

Most reviews present estimates of vaccine efficacy derived from studies in which principal outcome measures are 'confirmed' cases

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of influenza i.e. with laboratory-confirmation of infection. The reviews express results in relative terms (RR) (i.e. regardless of the level of influenza viruses circulating in the study population). The relative efficacy measure represents the capacity of the vaccine to prevent cases specifically due to virus strains contained in the vaccine compared to the control. When used in vaccination campaigns the same vaccines are unlikely to prevent the same proportion of cases simply because most ILI cases are attributable to other viruses. To assess the real benefit produced by a campaign it would be preferable to also look at the impact of the vaccines on ILI and to present results using absolute measure such as RDs and their reciprocal, the NNV. These take into account the level of influenza viral circulation in the population.

AUTHORS' CONCLUSIONS

Implications for practice

National policies for the vaccination of healthy young children are based on very little reliable evidence.

Implications for research

More randomised trials are required to test the efficacy of influenza vaccines, particularly of inactivated vaccines, in younger children. Further safety data should also be collected or made available of the safety of vaccines in children, particularly inactivated vaccine in younger children. There is an immediate need to standardise safety outcome data according to Brighton Collaboration Guidelines. Honest and full disclosure of all safety data to researchers is also a priority.

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* *Indicates the major publication for the study*

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[author-defined order]*

ab Aksenov 1971

Methods	Intra-pandemic, placebo-controlled CCT of live attenuated bivalent recombinant vaccine in school children in the Moscow area during the early part of 1969. Serological surveillance retrospectively showed that A2 Hong Kong caused most of the cases
Participants	School children from 2 boarding schools aged 4 to 7 years and 8 to 15 years. There does not appear to be any attrition
Interventions	Live attenuated injected vaccine containing A2 and B type antigens, made in the central Moscow laboratories
Outcomes	ILI, pneumonia, bronchitis, OM, tonsillitis and duration and severity of influenza
Funding Source	Government
Notes	The authors conclude that vaccination did not prevent cases but shortened duration and severity of illness. Unfortunately no standard deviations are reported for mean duration. The trial is reasonably reported but there probably is selection bias in serological testing

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Pseudo-random
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Number of losses to follow-up is unknown
Summary assessments	Unclear risk	Plausible bias that raises some doubt about the results

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aa Alexandrova 1986

Methods	C-RCT possibly followed by 2 cohort studies
Participants	Nearly 30,000 school children (aged 7 to 15) and preschool children (aged 3 to 6). The units sampled were schools and kindergartens. The samples were performed using random sampling numbers and stratified sampling in schools with different numbers of children. Initially reactogenicity of the vaccine was studied on a limited group of school children (190) and children between 3 and 6 years (267). After the low reactogenicity of the vaccine was assessed, vaccination of large groups of children was undertaken. The trial was extended to 45 schools (in 26 the bivaccine was administered, in 19 placebo) and to 142 community preschools (the children of 76 received vaccine, those from the other 66 received placebo). For each child a special form was completed in which data about immunisation and diseases were registered. No influenza was registered before the vaccination was carried out
Interventions	On a limited study population, (those vaccinated in October 1982), a reactogenicity study was separately carried out. This group consisted of 457 pupils and children, who were divided into 2 groups. One group was given vaccine, the other received placebo. Cases of mild, moderate or febrile reaction within 5 days of administration of vaccine or placebo were reported in consideration of the initial anti-HA antibody level. These data were not considered because it is most probable that the treatments were not assigned randomly
Outcomes	Incidence of influenza and acute respiratory disease during influenza epidemic 15 March to end April, 1983 Serological Antibody titres carried out on a non-random section of the study population Effectiveness The prophylactic effectiveness of the bivaccine was estimated during an influenza epidemic caused by viruses A/Brazil/11/78 H1N1 and A/Bangkok/1/79 H3N2 (similar to the strains employed in the vaccine), that started in the middle of March 1983 and lasted for 6 weeks. The comparison of the influenza morbidity rates among vaccines and control groups of children were based on clinical diagnosis during the epidemic period Safety A) The data on morbidity from acute respiratory diseases and tonsillitis within 5 days after first immunisation were analysed for 15,727 vaccinees and for 14,228 placebo recipients: 1) influenza and acute respiratory diseases, 2) bronchitis, 3) tonsillitis B) For the more susceptible age group of 3 to 6 years data were recorded for 6 months after the first dose of vaccine, with the exception of the 6-week period of influenza epidemic: 1) influenza and acute respiratory diseases, 2) pharyngitis, laryngitis, tracheitis, bronchitis, 3) pneumonia, 4) allergy, 5) otitis, 6) tonsillitis
Funding Source	Government
Notes	"There are three studies reported in this paper. The first is a phase 2, 5-day reactogenicity and safety trial carried out in 284 placebo recipients and 173 vaccine recipients. Although it claims randomisation, it is unclear why the imbalance in numbers and because of the unclear text describing what went on we classified it as a C-RCT. There appears to be an extension of the safety data to 14,228 placebo and 15,727 vaccine recipients

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aa Alexandrova 1986 (*Continued*)

	The second study (1 October 1982 to 14 march 1983) appears to be an extension of the first study assessing effectiveness in 3538 bivalent vaccine recipients and 3271 placebo recipients. However, in the absence of influenza viral circulation the vaccine appears to be highly effective against ILI, bronchitis, pneumonia, OM and tonsillitis A third study is the extension by 6 weeks (from 14 March 1983 of the second study) during the influenza epidemic. As the denominators are different in all three studies and there is no way to understand what went on, it is very difficult to classify study design."

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Cluster-randomisation: random sampling numbers and stratified sampling were used
Allocation concealment (selection bias)	Low risk	Both vaccine and placebo batches were coded
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Number lost to follow-up is unknown
Summary assessments	Low risk	Plausible bias unlikely to seriously alter the results

ca Allison 2006

Methods	5-practice retrospective cohort study taking place in Colorado during the 2003 to 2004 season. The study assessed the effectiveness of an undescribed vaccine in preventing ILI in healthy children aged 6 to 21 months. Participant's data and immunisation status were identified from reimbursement registers and a Web-based immunisation register. Analysed data come from the period 1 Nov to 31 Dec 2003, this is the period when influenza A circulated in a prevalent fashion according to hospital isolates. RSV started circulating at the end of Dec, so the authors attempted to restrict analysis to the period of maximum influenza circulation. This, of course, does not mean that other pathogens may not have been co-circulating. The results are presented for 2 peaks of ILI attendances, 1 corresponding with influenza A circulation and the other with RSV circulation ("influenza and RSV seasons")
Participants	5193 healthy children aged 6 to 21 months. The 21-month limit was chosen because of billing constraints. Participants were mostly white and privately insured. The authors classified participants as FV, PV or UV but as some UV became PVs and FVs as the season progressed, denominators are unstable. In addition FV includes those that had 1 dose from the previous season, further increasing the confusion. At 1 March 2004 when the study ended there were 2087 FV, 1040 PV and 2066 UV

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Interventions	1- and 2-dose vaccinations versus do-nothing. The vaccine must have been TIV which is the only one registered in this age group in the USA. No mention is made of content or matching
Outcomes	Serological N/A Effectiveness Physician's office attendance for: ILI or P&I as defined in ICD 9. These were assessed only for first visits to the family physician Safety N/A
Funding Source	Government
Notes	The authors conclude that "a total of 28% of the patients had an ILI office visit and 5% had a pneumonia/influenza visit. HRs for FV versus UV were 0.31 (95% CI 0.3 to 0. 4) for ILI and 0.13 (95% CI 0.1 to 0.2) for pneumonia/influenza, corresponding to a vaccine effectiveness (1 - HR 100) of 69% for ILI and 87% for pneumonia/ influenza. The corresponding HRs for PV versus UV were 1.0 (95% CI 0.9 to 1.2) and 1.1 (95% CI 0.8 to 1.5) Conclusions Although 2 doses of vaccine were 69% effective against ILI office visits and 87% effective against pneumonia/influenza office visits, 1 dose did not prevent office visits during the 2003 to 2004 influenza season." Summary estimates are presented as HR and the authors used a Cox proportional Hazards model, so no disaggregated numerators are available. As denominators are also moving the study results are difficult to interpret. Data are reported by influenza (ILI and P&I) and RSV (ILI) seasons. Asymmetrical reporting? It is difficult to assign a design to this study as the text is unclear on timings and buried in the text is the phrase "This study was conducted as part of a randomised controlled trial of registry-based reminder recall in 5 private paediatric practices in Denver, Colorado from September 1, 2003 through February 29, 2004 (Kempe A, Daley MF, Barrow J, Allred N, Hester N, Beaty BL, et al). Implementation of universal influenza immunisation recommendations for healthy young children: results of a randomised, controlled trial with registry based recall. Pediatrics 2005;115:146-54). There is also an implausible sharp division between influenza and RSV around New Year's Eve. High risk of bias

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
PCS/RCS-Selection Exposed cohort	Low risk	Selected group of users, secure records
PCS/RCS-Selection Non Exposed cohort	Low risk	From the same community as the exposed cohort
PCS/RCS-Comparability	Unclear risk	It is unclear whether the study took into account all possible confounders

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ca Allison 2006 (*Continued*)

PCS/RCS-Assessment of Oucome	Unclear risk	Physician's office attendance for: ILI or P& I as defined in ICD 9. These were assessed only for first visits to the family physician
Summary assessments	Unclear risk	No description of vaccine, content or matching, no disaggregate numerators by event and arm, unstable denominators, low generalisability of results

ba Anonymous 2005

Methods	Case-control study based on the 45 British Columbia surveillance system sites in which for 2004 to 2005 sentinel physicians were encouraged to take more swabs. Cases were participants who reported to sentinel physicians with acute onset respiratory illness with fever and cough and 1 or more of sore throat, arthralgia, myalgia or prostration and had a positive specimen for influenza A. Controls were all other symptomatic reportees who tested negative. Once the specimens were taken a questionnaire with details of the case was attached. The authors report that "there were 219 separate submissions of respiratory specimens by a known sentinel physician during the 2004 to 2005 surveillance period. Of these, only 32 (15%) had all questionnaire information completed on the original laboratory requisition; 187 required follow-up interview with the submitting physician to complete missing information and 133 were completed. From the 165 patients with complete records, specimens were collected between 4 October, 2004 and 31 March, 2005 with the distribution of submissions mirroring the distribution of sentinel visits for ILI overall"
Participants	165 out of 219 participants had enough information as required by the study protocol. Of these 134 were from the period of greatest circulation. 40 and 7 cases respectively had specimens positive for influenza A and B and only 7 overall were aged 19 or below. The text appears to suggest that matching was partial
Interventions	TIV (various suppliers) formulations were standardised to contain 15 µg each of A/H1N1/New Caledonia/20/99, A/H3N2/Wyoming/3/2003 (antigenically equivalent to A/H3N2/Fujian/411/2002) and B/Jiangsu/10/2003 strains
Outcomes	Laboratory Specimens were swabs or nasal washouts on which PCR was used
Funding Source	Government
Notes	The authors conclude that "We found age-adjusted point estimates for VE against medical consultation for laboratory-confirmed influenza A during the mismatched 2004 to 2005 season to range as low as 40% and as high as 75%. VE varied with age, definition of immunisation status and whether analysis was restricted to presentation within 48 hours of ILI onset. Overall, our estimates suggest cross-protection for the 2004 to 2005 season despite vaccine mismatch. Our VE estimates mostly reflect the protection conferred to young healthy adults; the sample included few elderly persons or those with underlying conditions. The higher than expected reports of facility outbreaks in 2004 to 2005 in BC may have reflected an even lower VE amongst the frail elderly. Because of small sample size, estimates are unstable with wide confidence intervals. The possibility of no protection cannot be ruled out". Attrition, small sample size, recall and performance bias. High risk of bias

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ba Anonymous 2005 (*Continued*)

Risk of bias		*Risk of bias*
Bias	**Authors' judgement**	**Support for judgement**
CC-Case Selection	Low risk	Independent validation and representativeness series of cases
CC-Control Selection	Low risk	Selected from the same population
CC-Comparability	Unclear risk	Only sex and age adjustment
CC-Exposure	High risk	No descriptions
Summary assessments	Unclear risk	Attrition, small sample size, recall and performance bias

ab Belshe 1992

Methods	RCT of safety vaccine, double-blind 0.5 ml of trivalent vaccine administered intranasally (as previously described, see notes for refs) Children observed in own homes for 11 days by nursing staff Daily sampling - nasopharyngeal swabbing for isolation of influenza virus Serum for antibody determination obtained on days 0 and 28 to 31
Participants	Healthy children age 6 months to 13 years
Interventions	Live, trivalent vaccine, recombinant containing A/Kawasaki/9/86 (H1N1) CR125 + A/Korea/1/82 CR59 + B/Texas/1/84 CRB-87 A/Kawasaki/9/86 and A/Korea/1/82 derived from cold-adapted A/Ann/Arbor/6/60 parent virus B/Texas/1/84 derived from cold-adapted B/Ann Arbor/1/66 parent virus
Outcomes	Adverse reactions up to 11 days after vaccination Fever: rectal temperature > 38.3°C (infants and young children); oral temperature > 37.8°C in older children) Upper respiratory illness: rhinorrhoea on 2 consecutive days; lower respiratory illness; wheeze or pneumonia; OM Viral shedding (data not extracted) Serologic response to vaccine (data not extracted)
Funding Source	Government
Notes	Safety data presented separately for seronegative and seropositive responders but has been combined for extraction. Was significantly (P < 0.5) higher upper respiratory illness in seronegative individuals than seropositive individuals

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ab Belshe 1992 (*Continued*)

Risk of bias		*Risk of bias*
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	High risk	Not used
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Summary assessments	High risk	Lack of allocation concealment; plausible bias that seriously weakens confidence in the results

aa Belshe 1998

Methods	Multicentre, prospective, randomised, double-blind, placebo-controlled trial to assess efficacy and safety of a cold-adapted influenza vaccine in single- and 2-dose regime versus placebo. Vaccine and placebo were randomly assigned sequential vaccination numbers. Randomisation sequence was incorporated in the preparation and labelling of materials. Each eligible child received the next available study number at a site, ensuring proper randomisation. Placebo was indistinguishable from the vaccine in appearance and smell
Participants	"Healthy children aged between 15 and 71 months at the time of their enrolment (August '96). A total of 1314 children were enrolled in the 2-dose group and 288 for the 1-dose. No statistical differences in age, sex, race, daycare and household makeup were observed between vaccine and placebo groups Subjects scheduled to receive 2 doses of vaccine; received the first between August 21, 1996 and October 23, 1996; the second dose between October 15, 1996 and January 11, 1997. Subjects in the 1-dose cohort were vaccinated between September 30, 1996 and December 5, 1996"
Interventions	Cold-adapted, trivalent influenza vaccine (supplied by Aviron, Mountain View, California). Vaccine reassortants contained the strains A/Texas/36/91-like (H1N1), A/Wuhan/359/95-like (H3N2), B/Harbin/7/94-like in egg allantoic fluid with sucrose, phosphate and glutamate. The mean dose of each attenuated strains was 106.7. These matched the antigens recommended for that year by the Food and Drug Administration (1996 to 1997) Placebo consisted only of egg allantoic fluid with sucrose, phosphate and glutamate Both were intranasal administered through a spray applicator (0.25 ml of placebo or vaccine per nostril) In the 1-dose group 189 participants were vaccinated and 89 received placebo; in the

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	2-dose group 881 participants were randomised to receive vaccine and 433 to receive placebo. From this group 42 participants didn't receive the second dose for the following reasons:
	• 2 withheld because they had adverse reactions after the first dose
	• 18 withdrawal of consent
	• 7 intercurrent illness
	• 12 violation of protocol or withdrawal by an investigator
	• 3 loss to follow-up or departure from the area and
	• 13 were excluded from the efficacy analysis (only for the 2 doses alone) because:
	  ○ 5 had received influenza vaccine outside of the study
	  ○ 8 were infected by influenza virus A (H3N2) before receiving the second dose
	1 case was in the vaccine recipients and seven among the placebos
	All these 55 (and the eight cases of influenza A) were included in the efficacy analysis considering the 2 groups together

Outcomes	Serological Hemagglutination Inhibiting Antibody Responses After 1 or 2 doses of vaccine or placebo were evaluated. Data for 136/849 (2 doses recipients) vaccinated only reported - likely SELECTION BIAS Effectiveness Influenza defined as any illness detected by active surveillance associated with positive culture for wild type influenza virus 28 days after the first dose and any time after the second dose during the influenza A H3N2 and B epidemic, that lasted up to April 1997. After the outbreak of influenza in the community (end November 1996) parents were contacted and reminded to notify if the subject had symptoms suspected to be caused by influenza: fever, runny nose, nasal congestion, sore throat, cough, headache, muscle aches, chills, vomiting, suspected or confirmed OM, decreased activity, irritability, wheezing, shortness of breath and pulmonary congestion. It was attempted to collect viral culture specimens within four days after the onset of any illnesses Safety The parent or guardian of each subject was given a digital thermometer and asked to record on a diary card temperature (fever was defined as an axillary temperature above 37.6°C or oral temperature above 37.7°C or rectal temperature above 38.1°C) and occurrence of specific symptoms including decreasing activity, irritability, runny nose or nasal congestion, sore throat, cough, headache, muscle aches, chills and vomiting, daily for 10 days after each vaccination
Funding Source	Government/Industry
Notes	The authors conclude that live attenuated, cold adapted influenza vaccine is safe, immunogenic and effective against influenza A and B in healthy children. Vaccine efficacy is equally high for older and younger children

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Block randomisations (block size of six)

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aa Belshe 1998 (*Continued*)

Allocation concealment (selection bias)	Low risk	"The randomisation sequence was incorporated in to the preparation and labelling of materials, and each eligible child received the next available study number at a site"
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Few losses of follow-up
Summary assessments	Low risk	Plausible bias unlikely to seriously alter the results

aa Belshe 2000a

Methods	See aa Belshe 1998
Participants	1358 healthy children who previously participated in year 1 of trial (aa Belshe 1998). Aged 26 to 85 months
Interventions	Re-vaccination with live attenuated, cold-adapted trivalent (H1N1, H2N3 and B) influenza vaccine, administered by nasal spray
Outcomes	1. Primary end-point of efficacy: first episode of culture-confirmed influenza occurring in an individual child after revaccination 2. Subtype specific efficacy (A and B) 3. Influenza: any illness detected by active surveillance associated with positive culture for wild-type influenza virus 4. Strain-specific antibody responses to vaccine 5. Adverse reactions: increase in temperature, decreased activity, irritability, runny nose or nasal congestion, sore throat, cough, headache, muscle aches, chills, vomiting, OM 6. Serious adverse events occurring at any time during the study 7. Incidences of flu-like illness detected by surveillance
Funding Source	Government/Industry
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Second year of study of aa Belshe 1998 not re-randomised

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aa Belshe 2000a (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Second year of study of aa Belshe 1998, not sufficient description
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	At the start of the second study year (aa Belshe 1998) only 86% in the treatment arm and 83% in the placebo arm, from the first study year (aa Belshe 1998) were enrolled but insufficient information given to the end of this second study year
Summary assessments	High risk	Plausible bias that raises some doubt about the results

aa Beutner 1979a

Methods	Randomised, placebo-controlled trial to assess antibody response, efficacy and safety of a neuraminidase-specific influenza vaccine. Subjects were randomly divided into three groups to receive a single dose of 1 preparation (X - 41, X - 42 or placebo) under code
Participants	Study population consists of 875 healthy children of both sexes aged 7 to 14 years, who were recruited from the public school system, after written informed consent for immunisation was obtained from the parents
Interventions	• "X - 41 Inactivated Port Chalmers (H3ChN2Ch) influenza vaccine • X - 42 Inactivated recombinant influenza vaccine containing equine hemagglutinin (HEq) and an A2 Port Chalmers neuraminidase • Placebo consisting of vaccine diluent only Hemagglutinin titres were determined by the method of Horstaff and Tamm and were 1024 for X - 41 and 3072 for the X - 42 X - 41 vaccine contains 2.3 fold greater neuraminidase activity than X - 42 All recruited children were intramuscularly inoculated with 1 0.5 ml dose of vaccine or placebo between September and November 1974. Serum samples were obtained before and at regular intervals after vaccination
Outcomes	Serological Antibody titre rise Effectiveness "Influenza infection assessed during 2 epidemics. The first of these lasted between mid December 1974 and April 1975 and was due to the Port Chalmers (H3Ch N2 Ch) strain. An outbreak of Victoria strain was also observed in the population from January to March 1976. Serum samples were obtained before and at regular intervals after vaccination for determination of antibody response (1, 2, 6 months after vaccination). Clinical illnesses in the vaccinated were also evaluated by examination of all sick children within 24 hours during the subsequent outbreaks of natural influenza infection A minor outbreak of Victoria strain occurred in Buffalo from January to March 1976. Most of the immunised children were available for evaluation during this epidemic (220 in the X - 41 group, 200 in the X - 42 group, 185 in the placebo group)." Safety

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aa Beutner 1979a (*Continued*)

	"Data on reactogenicity of influenza immunisation were obtained through telephone calls and questionnaire mailed to the parents of the vaccinees. All children reporting any reactions were immediately examined by a physician and evaluated for the degree of reactogenicity. Follow-up for vaccine reactions was carried out for 1 to 4 weeks after vaccination. Data about local (pain-tenderness, erythema, swelling, none) and systemic reactions (headache, nausea-vomiting, soreness-aching-chills, none) are reported"
Funding Source	Government
Notes	"The authors conclude that both vaccines work as well as the bivalent"

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random number
Allocation concealment (selection bias)	Low risk	Coded identical looking compounds
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up
Summary assessments	Low risk	Plausible bias unlikely to seriously alter the results

aa Beutner 1979b

Methods	See aa Beutner 1979a
Participants	
Interventions	
Outcomes	
Funding Source	
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**

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aa Beutner 1979b (*Continued*)

Random sequence generation (selection bias)	Low risk	Random number
Allocation concealment (selection bias)	Low risk	Coded identical looking compounds
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up
Summary assessments	Low risk	Plausible bias unlikely to seriously alter the results

ca Burtseva 1991

Methods	Prospective cohort study of efficacy of live recombinant and inactivated influenza A (H3N2) vaccines versus placebo-cold-adapted recombinant live influenza vaccine A/47/F (H3N2) obtained by method described in other papers (Medvedeva et al, 1989. Vopr. Virusol.; 34: 564-8 and Alexandrova et al. 1984. Infect. Immun.; 44: 734-9) • Virus A/Philippines/2/82 (H3N2) used as epidemiological strain • Doctors notes collected from children absent in school 1 between 1/1/88 and 1/3/88 to find diagnoses of acute respiratory illness or influenza • Blood samples taken from recovering children in school 1 • Blood samples taken from all children under observation before epidemic in January 1988 and 2 months after end of epidemic in April, 1988 • Blood serum tested for inhibition of haemagglutinin for seroconversion to A/Philippines/2/82 (H3N2) and B/Victoria/2/87 (H1N1) • Children in school 1 re-immunised in autumn 1988 with live influenza vaccine A/47/S produced by hybridisation of between cold-adapted donor virus A/Leningrad/134/47/57 (H2N2) and a new drift variant of influenza A (H3N2) A/Sichuan/2/87 • 4 groups of children received the following interventions: 1 - live vaccine both years; 2 - inactivated vaccine in year 1 and live vaccine in year 2; 3 - placebo year 1 and live vaccine year 2; 4 placebo both years • Nasopharyngeal swabs taken from 41 children in various groups at 2, 3 and 8 days after vaccination, inoculated into chicken embryos and tested for hemagglutination. If no hemagglutination observed in on first test, was repeated at least 3 times. Antigenic structure of surface glycoproteins was defined in isolated strains • Paired serum samples taken from children revaccinated with A/47/S (H3N2) and tested for hemagglutination with antigens A/47/S (H3N2), A/Philippines/2/82 (H3N2), A/Taiwan/1/86 (H1N1) and B/Victoria/2/87 • School 1 - outbreak of influenza B (B/Victoria/2/87) occurred Dec 87 - Jan 88 and influenza A (H3N2, close to A/Sichuan/2/87) occurred Jan to Feb 88. Determined by 4-fold increase in antibodies from sub-samples of children tested • School 2 - epidemiological rise in from 3rd week January then continued until 3rd week Feb, 89% of confirmed influenza cases were A (H3N2) and only 11% were B
Participants	Children aged 8 to 15 years

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ca Burtseva 1991 (*Continued*)

Interventions	1. Cold-adapted recombinant live influenza vaccine A/47/F (H3N2) - infectious titre 7.0 1 EID50/0.2cc - administered intranasally using Smirnov apparatus 2. Inactivated influenza vaccine containing strains similar to A/Philippines/2/82 (H3N2) and A/Chile/1/83 (H1N1) containing 10 μg of haemagglutinin of each strain in 0.5 ml dose - administered subcutaneously in upper third of shoulder 3. Live influenza vaccine A/47/S; hybrid of cold-adapted donor virus A/Leningrad/134/47/57 (H2N2) and A/Sichuan/2/87 (H3N2) - infectious titre 7.3 1 g EID50/0.2cc - re-immunisation
Outcomes	1. Cases of acute respiratory illness or influenza in school 1 between 1/1/88 and 1/3/88 (excluding confirmed influenza B diagnosis) i.e. during influenza A(H3N2) outbreak period 2. Cases of laboratory-confirmed influenza (H3N2) in school 2 between 16/1/88 and 15/2/88 (excluding confirmed influenza B diagnosis) 3. Re-isolation of virus (not for data extraction) 4. Rise in antibody titre in children inoculated with vaccine strain A/47/S in year 2 (not for data extraction) 5. Slight increase in temperature (not extractable - no placebo data given) 6. Subjective events (not extractable - no placebo data given)
Funding Source	Government
Notes	The authors conclude that bivalent vaccine had better performance (they report protection indices) but the text has so many contradictions, lacks clarity and mentions exclusion of influenza B cases from the analysis that it is impossible to understand what went on. Children from 'internat' roughly translates as state orphanage, could be ethical issues surrounding consent

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
PCS/RCS-Selection Exposed cohort	Unclear risk	No description
PCS/RCS-Selection Non Exposed cohort	Unclear risk	No description
PCS/RCS-Comparability	Unclear risk	No description
PCS/RCS-Assessment of Oucome	Unclear risk	No description
Summary assessments	High risk	Plausible bias that raises some doubt about the results

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ca Chumakov 1987

Methods	Prospective cohort study, re-analysis of data from Bashliaeva 1986, which did not take into account that influenza vaccine not intended for prophylaxis of other ARIs, which make up about 70% of total and found repeatedly in children aged 3 to 6 years • 'Full formation of immunity can only be expected in children 1 month after second dose. So desirable that vaccination should be completed no later than 1 month before beginning of epidemiological rise in cases of viral influenza.' Authors claim this condition was not observed in Baslyaeva 86 study causing reduction in children vaccinated twice who had prepared immune status before beginning of influenza outbreak • Claim figures for numbers of children inoculated in Bashlyaeva 86 are wrong, caused by error in calculation and designation of groups. Bashlyaeva 86 did not report that 411 inoculated children were eliminated from the observations for various reasons and should be excluded from the analysis The authors claim that inoculations began late when an epidemic situation has already arisen and numbers of children attending nurseries had dropped by the time the second vaccination was administered (to a comparatively smaller number of children). The authors claim that antigenic activity was incorrectly analysed
Participants	See Bashliaeva 1986 - 2274 children were inoculated once with the 2 types of the vaccine, 876 were inoculated twice; 1321 and 573 children were inoculated with placebo, respectively
Interventions	See Bashliaeva 1986 - 2 types of the vaccine were tested (15 and 16). The vaccines contained three strains (A/Brazil/11/78 (H1N1), A/Bangkok/1/79 (H3N2) and B/Singapore/222/79). The total amount of the B haemagglutinin varied: 31.9 μg (Type 15) and 29.2 μg (Type 16). The vaccines also contained ovalbumin (Type 15 was 0.125 μg/ml, in Type 16 it was 0.06 μg/ml). Sterile, apyrogenic, physiological solution was used for placebo. Vaccines or placebo were administered subcutaneously; 2 doses of 0.5 ml, with an interval of 28 to 30 days
Outcomes	Effectiveness: Cases of ARI and influenza Influenza and ILI. There are 2 statements on assessing the impact of influenza "With the aim of serologically analysing the clinical diagnoses of influenza and acute respiratory illnesses from the children who fell ill during the period of observation, 470 coupled samples of serum were taken (I -in the first days of illness, II- 18 to 20 days later)" and "In order to analyse the aetiology of the spread of the virus, 380 children were observed who had contracted influenza or acute respiratory illnesses, both those who had received the vaccine and those who had received placebo. The division of viruses of influenza was determined from swabs taken from the nose and throat area, implanted onto chicken embryos and the subsequent identification of that which had been isolated" Serology There are 2 apparently contradictory statements concerning serology and partly safety assessment. "The reactogenicity and antigenic activity of the vaccine were studied by observing the 305 vaccinated children and the 237 children who had received the placebo in 15 schools. They were assessed according to a series of well known indices, characterising the frequency and intensiveness of the local and general reactions to the vaccination" and "in order to study the antigenic activity of 'Grippovac SE-AZH', 320 samples of serum were taken from the inoculated children before vaccination, 280 samples were taken 21 days after the first injection and 170 samples were taken 21 days after the second

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ca Chumakov 1987 (*Continued*)

	injection". The reasons for his apparent attrition are unclear Safety See above. Other harms data (headaches etc. are reported as 1-liner with no data)
Funding Source	Government
Notes	The authors report that there was a significant difference in the level of response in immunity in the recipients of Type 15 (45.8%) and Type 16 (76%) towards the serotype A (H1N1) probably due to vaccine antigen concentration and concluded that "the preparation showed insignificant reactogenicity and moderate antigenic potency. The trial established that at the period of the epidemic rise of influenza B morbidity the vaccine showed, according to the data of the clinical diagnosis of influenza, insignificant effectiveness, its index of effectiveness (IE) being 1.08; according to the data of the serological diagnosis of influenza, only the A (H1N1) component of the vaccine was found to have IE equal to 1.58". This was a very difficult text to follow with many inconsistencies. Allocation and blinding are not described denominators are not clear. See also criticism by Chumakov et al in Chumakov 1987

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
PCS/RCS-Selection Exposed cohort	Low risk	Somewhat representative, secure record
PCS/RCS-Selection Non Exposed cohort	Low risk	Drawn from the same community
PCS/RCS-Comparability	Unclear risk	Only by age
PCS/RCS-Assessment of Oucome	Unclear risk	No descriptions
Summary assessments	Unclear risk	Plausible bias that raises some doubt about the results

aa Clover 1991

Methods	Multicentre, cluster-randomised, placebo-controlled clinical trial in which the efficacy of bivalent cold adapted and trivalent inactivated influenza vaccines were compared. Seventy per cent of the study population had already been immunised in the previous "Gruber 90", whose participants were enrolled at the same centres and that was carried out during the previous year. Design and methods of enrolment are similar to those adopted in that study (see linked studies list)
Participants	103 families were enrolled from Houston Family Study, Baylor Family Practice Clinic (Houston) and Family Medicine Clinic (University of Oklahoma). They were randomly assigned to receive placebo (40%) or 1 of the 2 vaccines (each 30%). About 70% of the families were enrolled and randomised the previous year and received the same preparation. The entire study population consisted of 166 adults and 225 children. Ninety-eight families with 157 adults and 192 children aged almost 3 years and 20

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aa Clover 1991 (*Continued*)

	children younger than 3 years completed the study
Interventions	Bivalent cold recombinant influenza A vaccine containing 107 TCID50 of CR - 90 (A/Bethesda/1/85 H3N2) and 10 7 TCID 50 of CR - 98 (A/Texas/1/85 H1N1) in 0.5 ml. 1 dose intranasally administered • Trivalent, inactivated influenza vaccine (standard licensed Fluogen, Parke Davis, Detroit) containing 15 μg of each A/Chile/83 H1N1, A/Missisipi/85 (H3N2) and B/Ann Arbor/86 hemagglutinin antigen in 0.5 ml. 1 dose intramuscularly administered • Placebo consisted of buffered or sterile saline, which were administered respectively intranasally or intramuscularly. Subjects in the placebo arm were randomised to receive one or the other preparation
Outcomes	Serological Children receiving vaccine or placebo, were brought in 3-4 weeks after vaccination to obtain a second blood specimen to determine antibody responses to vaccine antigens. However, paired sera were taken from 112 children with no explanation as to why Effectiveness • "Influenza A infection • Febrile illnesses (with temperature >38°C) : including upper or lower respiratory tract illness, otitis media, influenza-like illness • Afebrile illnesses When ongoing community surveillance at the Influenza Research Center indicated that influenza virus was spreading in the community (influenza A/Taiwan/86), weekly telephone contacts to families were made to evaluate respiratory illnesses. Home or clinic visits were scheduled for physical examination and collection of nasal washes or swab specimens for viral isolation. An illness was attributed to influenza A infection if influenza virus was isolated during the illness or , for a person with a postseason antibody rise only, if no other virus was detected in the illness specimen and if the illness occurred within 10 days of an isolate in household contact or during the period of most intense influenza activity in the community. Illnesses were characterised by review of records which included date of onset, symptoms, physical signs diagnosis of each contact." Safety N/A
Funding Source	Unclear
Notes	The authors conclude that TIV gave a better protection against detectable infection in older children (P > 0.1 TIV vs placebo) than CR vaccine, who instead were more protective in younger children (based however on a denominator of 27, 35 and 51 CR, TIV and placebo recipients). There were no statistical differences in infection rates for family contacts of children receiving TI or CR or placebo Analysis seems to have been done at individual level, whereas randomisation was at cluster level. The authors report that the vaccines were ineffective at preventing transmission

Risk of bias			***Risk of bias***
Bias	**Authors' judgement**	**Support for judgement**	

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aa Clover 1991 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	No description
Allocation concealment (selection bias)	Unclear risk	Not used
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Few losses to follow-up, unlikely to be related to true outcome
Summary assessments	Unclear risk	Plausible bias that raises some doubt about the results

aa Colombo 2001

Methods	Randomised open trial to assess the efficacy of a trivalent subvirion vaccine
Participants	Healthy children from the area of Sassari (North Sardinia). All were aged 1 to 6 years and none had ever been immunised against influenza. Children with hypersensitivity reactions to eggs were excluded. Of the 398 meeting the inclusion criteria, 344 accepted to participate. 177 were randomly assigned to receive trivalent subvirion vaccine, 167 to the control group (no treatment)
Interventions	Trivalent subvirion influenza vaccine (Agrippal, Biocine S.p.A.) containing 15 microg of the high purified surface antigens from the following component strains : A/Johannesburg/33/94-like, A/Singapore/6/86-like, B/Beijing/184/93-like. 2 doses 1 month apart were administered. Subjects immunisation took place between October 15 and November 15 , 1995 • No treatment
Outcomes	Serological Paired sera for 17 participants, to test seroconversion and not diagnose influenza Effectiveness • "Influenza-like illness Follow-up was carried out between December 1, 1995 and April 30, 1996. No participants were lost during this time. All children who developed influenza-like symptoms were seen by the paediatrician. A clinical examination was conducted and repeated at the end of the illness with the aim to collect information regarding the duration of clinical symptoms and daycare absenteeism (also for the family members). Influenza-like illness was defined as rectal temperature above 38.5°C and cough or sore throat lasting at least 72 hours" Safety • "Systemic reactions (fever) • Local reactions (erythema at the injection site) • Parents were asked to contact the paediatrician in case of adverse event"

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aa Colombo 2001 (*Continued*)

Funding Source	Government
Notes	The authors conclude that killed influenza vaccine is safe and effective in preschool children. Data about the rate of infection in parents were reported but it is not possible to state the number of parents involved. Only 85.5% of the children in the control group and 89.2% in the vaccinated group were in a daycare centre • Quality of randomisation is suspect (different prevalence on passive smoking in the arms), lack of serological diagnosis despite 17 sera taken for seroconversion, no mention of circulating viruses in the season

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated list
Allocation concealment (selection bias)	High risk	No description
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses
Summary assessments	High risk	Plausible bias that seriously weakens confidence in the results

ab Desheva 2002

Methods	RCT of adult variant (single-dose) of live influenza vaccine in children aged 3 to 6 years. Two groups of children were formed to receive vaccine, 1 to receive placebo. Paediatricians from clinics serving nurseries selected children for immunisation. Parental consent was obtained for each child. Medical examination of children was carried out each day for 5 days after inoculation - body temperature measured; local and general reactions recorded • Re-isolates obtained from vaccinated children 3 days after inoculation to determine genetic stability of viruses using PCR restriction analysis • Morbidity was studied for 6 months after inoculation - based on data from medical records which included influenza and acute respiratory illnesses and registration of somatic and infectious diseases
Participants	Children aged 3 to 6 years from nursery schools in the St Petersburg area
Interventions	Trivalent, live influenza vaccine contained WHO recommended strains for 1999 to 2000 - A/17/Peking/95/25 (H1N1), A/17/Sydney/97/76 (H3N2) and B/60/St-Petersburg/95/20. Vaccine or placebo (allantoic fluid from chicken embryos) were administered once intranasally using RDZH-M4 sprayer (0.25 ml per nostril). The difference between

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ab Desheva 2002 (*Continued*)

	children and adult vaccines is the number of times passed at lower temperature and in the number of mutations of the base attenuated donor strains A(H1N1) and A(H3N2)
Outcomes	Serological Paired serum samples were taken from subgroup prior to inoculation and 21 days after and analysed for haemagglutinin inhibition Effectiveness ILI, bronchitis infections, somatic illness and allergic pathologies (the last 2 are difficult to understand and have not been extracted Safety Fever (in different temperature breakdowns), headache and catarrhal symptoms
Funding Source	Government
Notes	The authors conclude that the vaccine is safe and effective. We do not think the data support this conclusion as for example the vaccine does not prevent against bronchitis. No viral circulation in community is described

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No description
Allocation concealment (selection bias)	Low risk	Coded preparations
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up
Summary assessments	Low risk	Plausible bias unlikely to seriously alter the results

ca El'shina 2000

Methods	Report of a 2-phase pilot RCT carried out in 1997 to 1998 among Moscow school children to assess safety of live attenuated trivalent vaccine ("Grippol"). The comparator was standard care. As usually happens in reports from Russia, there is a third study nested in the text. The study of cohort design was school based and assessed effectiveness against ILI. Data on general morbidity (excluding influenza and ARI) collected over entire observation period to determine possible side effects. Efficacy evaluated by comparing morbidity due to influenza and ARI using co-efficient of efficacy

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Participants	In the first study 2 groups (aged 14 to 17 years) were formed by randomisation. Both groups had 30 participants. In the second study 40 children aged 6 to 14 were again randomised to Grippol or standard care. The cohort study was carried out in three schools located near each other with a relatively similar level of morbidity and a comparable number of pupils. The school with a total number of 1835 students was assigned to the intervention group and 2 schools with a total number of 1315 individuals were assigned to the control group. However in the schools which had been assigned to the intervention group, "930 individuals were inoculated in the pre-epidemical season. The remaining 905 pupils were also practically entirely healthy at the time of the inoculations but remained UV due to temporary medical exclusions. They acted as the so called 'internal' control group"
Interventions	"The influenza tri-valent polymer-subunit 'Grippol' vaccine was created in the State Scientific Centre (the Institute of Immunology, the Ministry of Health for the Russian Federation) (7, 10). The preparation belongs to a new generation of vaccines. It is a sterile preparation, based on highly pure surface proteins of the influenza viruses A and B - hemagglutinins and neuraminidases. They are protective antigens (6). It is also based on synthetic high-molecular immuno-stimulator polyoxidonium, which has an adjuvant activity (10). 'Grippol' differs from other subunit influenza vaccines in the world because of its antigenic load, which is reduced by 3 times because of the inclusion of an immuno-stimulator. The inoculation dose of the 'Grippol' vaccine contains 5 μg of hemagglutinin of each strain of the influenza virus and 500 μg of polyoxidonium". No mention of matching nor of content is made
Outcomes	1. Influenza and ARI during period of seasonal rise in cases of influenza and ARI (12/97 to 04/98) 2. Influenza during period of seasonal rise in cases (12/97 to 04/98) only 60.4% serologically confirmed 3. General and local reactions to vaccination >/= 5 days (local reactions excluded as no placebo administered for comparison) 4. Somatic and infectious morbidity (excluding influenza and ARI) during period of seasonal rise in cases (12/97 to 4/98) "From December to April, monthly collections and analysis of data for the morbidity of influenza and acute respiratory illnesses were organised in the working and control groups. Moreover, in order to correct the clinical diagnoses, the selective serological decoding of cases of illness diagnosed as influenza and acute respiratory illnesses was carried out". Table 3 reports ILI for the 930 in the intervention cohort and their 905 controls out of a total of 1835 and 1315 school children respectively. This also includes "serological confirmation in 60.4% of cases"
Funding Source	Government
Notes	• The authors conclude that Grippol is safe and effective and recommend immunisation of children. The extensive contradictions between text and figures, unexplained selective serological testing and vaccination make this a high risk of bias study • Figure for serologically confirmed is 60.4% of calculated per 1000 figure for number with influenza and ARI. Therefore serological confirmation is an estimate not an absolute figure and it may not be appropriate to include in meta-analysis of

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ca El'shina 2000 (*Continued*)

	serologically confirmed influenza • Tables show period of seasonal rise from 07/97 to 04/98, likely to be mistake. Text refers to period from December 1997 to April 1998

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
PCS/RCS-Selection Exposed cohort	Unclear risk	Insufficient description
PCS/RCS-Selection Non Exposed cohort	Unclear risk	Insufficient description
PCS/RCS-Comparability	Unclear risk	Insufficient description
PCS/RCS-Assessment of Oucome	High risk	No description
Summary assessments	High risk	Plausible bias that seriously weakens confidence in the results

ca Fujieda 2006

Methods	Prospective cohort study carried out in 54 clinics around Japan during the 02 to 03 season. The study assessed the effectiveness of TIV against ILI. Baseline questionnaires were filled in at enrolment and then an "attack" questionnaire in which every week for 17 weeks parents recorded children's body temperature in 3 steps of 1°C There authors report ILI surveillance Japan-wide with peak isolates of A and B viruses in Jan to Feb. The authors describe an analysis stratified by age and other potential confounders (which are reported in Table 1). Systematic differences in age, birth and current body weight, number of siblings, family members, number and space in rooms etc are significantly different between hemicohorts
Participants	2913 children (1512 vaccinees and 1401 non-vaccinees) under 6 years of age (52% males) . Allocation was on an alternation basis according to the provision of parental informed consent and the following child whose parents did not give consent was allocated to the control arm. Attrition is not mentioned. Data by age group and location are reported but not extracted
Interventions	TIV (A/New Caledonia/20/99(H1N1), A/Panama/2007/99(H3N2) and B/Shandong/7/97) or no vaccination in 1 or 2 shots according to age. Producer not described. Matching not reported
Outcomes	Serological N/A Effectiveness ILI: acute febrile illness occurring during the highest epidemic period in each study area (but it is ILI, not influenza as claimed by the authors). Fever reported as below 38°C, between 38°C and 39°C, and 39°C or more (but no description of how temperature was taken by parents or whether follow-up was complete)

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ca Fujieda 2006 (*Continued*)

	Safety N/A
Funding Source	Government
Notes	The authors conclude that the adjusted OR and its 95% CI were calculated by the proportional odds model using logistic regression with 3-level outcome variables (< 38. 0/38.0 to 38.9/> or = 39.0 degrees C). A significantly decreased OR of vaccination was observed (OR: 0.76; 95% CI 0.66 to 0.88), corresponding to a vaccine effectiveness (1-OR) of 24% (95% CI 12% to 34%). When the analysis was confined to those aged > or = 2 years, a more pronounced OR (0.67; CI 0.56 to 0.79) was obtained with a vaccine effectiveness of 33% (21% to 44%). On the other hand, no significant vaccine effectiveness was detected among very young children; the ORs were 1.84 (CI 0.81 to 4.19) for those < 1 year of age and 0.99 (CI 0.72 to 1.36) for those 1.0 to 1.9 years of age and 1.07 (CI 0.80 to 1.44) when these 2 age groups were combined. Thus, among very young children vaccine effectiveness could not be demonstrated Lack of description of matching, unacceptable ILI definition (fever only), recall bias, measurement bias, unknown attrition, systematic differences between hemicohorts etc. make the study at high risk of bias. Of note in the Results is the reporting of the range of percentage of A and B isolates in each study area as a proportion of samples submitted during the height of the epidemic by sentinel physicians from symptomatic cases: 3% to 61%. In other words if data from this non-random sampling is generalisable, up to 97% of ILIs were not due to influenza

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
PCS/RCS-Selection Exposed cohort	Unclear risk	Volunteer
PCS/RCS-Selection Non Exposed cohort	Unclear risk	Volunteer
PCS/RCS-Comparability	High risk	Several difference between groups at baseline
PCS/RCS-Assessment of Oucome	Low risk	Secure record
Summary assessments	High risk	Plausible bias that seriously weakens confidence in the results

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bb Goodman 2006

Methods	Industry funded case to control study conducted among healthy children of both sexes who were part of a HMO (or group practice?) - HPMG - in Minneapolis, USA. The study was conducted to assess the safety of split TIV in small children after the 2002 decision by ACIP to extend the immunisation to this age group and study data spans 2 "seasons": 2002 to 03 and 2003 to 04. There is no declaration of conflicts of interest of the authors Cases Healthy children aged 6 to 23 for 1 or more days during the TIV administration period enrolled in the HPMG for 1 day or more during the study period and had 1 or more diagnostic code for a HPMG clinic during the study period Controls Children with same eligibility criteria matched by birth date and gender
Participants	13,383 children of which 3697 received vaccination
Interventions	TIV or no vaccination. Ascertainment of exposure was carried out through HPMG registry but no description of content or lot is given although the authors report that this information is available. For the effectiveness 1-liner no description of community viral circulation is reported. The authors report that they carried out multivariate modelling to allow for the effects of co-administration of other vaccines
Outcomes	Effectiveness Influenza 1 liner - no case definition given although it appears to be based on ICD 9 which means ILI Safety The following outcomes were identified either by physicians combing the exposed population for possible outcomes of interest and then clustering the diagnosis by ICD categories and then using VSD categories: ○ Purpura (window of observation - days after immunisation 0 to 42) ○ White blood cell disorders 0 to 42 ○ Rheumatic diseases 0 to 42 ○ Nephrotic syndromes 0 to 42 ○ Alopecia 0 to 42 ○ Urticaria 0 to 3 ○ Muscle weakness 0 to 42 ○ Myalgia 0 to 42 ○ Neuralgia 0 to 42 ○ Seizures 0 to 42 ○ Polyarteritis 0 to 42 ○ Myoglobinuria 0 to 42
Funding Source	Industry
Notes	The authors conclude that "We found no statistically significantly elevated hazard ratios for the first TIV dose. An elevated risk of pharyngitis was found for children receiving a second TIV dose. No elevated risk of seizure was found. CONCLUSION: These results, for a population of healthy children, showed no medically significant adverse events related to TIV among children 6 to 23 months of age" Definitions of cases and controls are not reported and were reconstructed by the extractor. More worrying is the fact that the text clearly states that the authors identified the cases by looking at outcomes AND exposure almost certainly introducing bias in the evaluation and not carrying out blinded assessment of exposure. Numerators and denominators are not reported by case and control status but only HR by first or second TIV injection. Population was selected and there are very few data to compare cases and controls. 1 liner by-the- by effectiveness assessment of vaccine. Multivariate modelling use is unclear. How can you adjust for

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bb Goodman 2006 (*Continued*)

	the effects of many concurrent vaccines if you do not have a non-exposed window and the safety outcomes are highly unspecific (e.g. urticaria)? High risk of bias

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
CC-Case Selection	High risk	No description
CC-Control Selection	High risk	Insufficient description
CC-Comparability	Unclear risk	No descriptions
CC-Exposure	Low risk	Secure record
Summary assessments	High risk	

ab Grigor'eva 1994

Methods	Placebo-controlled randomised trial of safety and effectiveness of live vaccine carried out in Havana, Cuba (with the collaboration of scientists from the former USSR) during the 1991 to 1992 season. The unit of allocation in schools was 1 child. The trial had five arms: 1 - inoculated with A(H1N1) vaccine; 2 - inoculated with A(H3N2) vaccine; 3 - inoculated with B vaccine; 4 - inoculated with trivalent vaccine A(H1N1)+A(H3N2) +B; and 5 - placebo. Morbidity studied during period 1 Dec to 31 Dec 1991. The period of epidemic was defined according to serological data and epidemiological curves. Calculation of morbidity based on clinical diagnosis of influenza and ARI
Participants	3663 children aged 5 to 14 years
Interventions	Live influenza vaccines, industrially produced series: A (H1N1), strain A/47/T (epidemical virus A/Taiwan/1/86, attenuated donor A/Leningrad/134/47/57); A (H3N2), strain A/47/6/2 (epidemical virus A/Zakarpatye/354/89, attenuated donor A/Leningrad/134/47/57); and B strain B/60/32 (epidemical virus B/USSR/3/87, attenuated donor B/USSR/60/69
Outcomes	Serological "Immogenicity - seroconversion - assessed on a sample basis (rule for sample selection not reported) Recombination analysis of genetic stability" Effectiveness Morbidity due to influenza and acute respiratory viral infections according to a variety of symptoms and signs (essentially ILI). Only effectiveness of the 2 does schedule was analysed. Background viral circulation was also assessed as well as data from seroconversions Safety The following outcomes were recorded: temperature, general ill-health, dysphonia, reddening of the throat, nasal bleeding, conjunctivitis, cough. Safety was assessed on the

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ab Grigor'eva 1994 (*Continued*)

	basis of sampling (rule for sample selection not reported). Clinical examinations were carried out for 4 days after each vaccination to record temperature, examination of integuments, nasopharynx and eye mucous and any complaints examination of integuments, nasopharynx and eye mucous and any complaints
Funding Source	Government
Notes	The authors conclude that live attenuated "polyvalent" vaccine are effective but no more than monovalent. Poor reporting (no description of blinding, placebo content and aspect, attrition etc) and likely selection bias of safety and immunological samples. However, there is a fairly detailed description of background viral circulation in Havana during Jan to Dec 1991 and an attempt at putting the results into this context. The authors show that there was no significant difference in morbidity between mono and polyvalent vaccine arms (49.7% in placebo arm vs 32.04% in arm 1 vs 28.29% in arm 2 vs 31.52% for arm 4 - the trivalent vaccine

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No description
Allocation concealment (selection bias)	Unclear risk	No description
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	No description
Summary assessments	Unclear risk	Plausible bias that raises some doubt about the results

aa Grigor'eva 2002

Methods	Placebo-controlled randomised trial carried out in 2 schools in the Lomonosovskii area and 2 schools in the Gatchinskii area, both in the Leningrad region, former USSR. There were six arms formed using a random selection method: 2 groups were inoculated with the Live Influenza Vaccine I; 2 groups were inoculated with the Live Influenza Vaccine II; and there was 1 placebo group for each vaccine. The unit of selection was 1 individual. The vaccine and placebo were administered as coded preparations. The influenza epidemic of the 1999 to 2000 season was caused by the influenza virus type A/Sydney/5/97 (H3N2)
Participants	2486 healthy children aged between 7 to 14 years during the 1999 to 2000 season

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Interventions	Child and adult variants of the Live Influenza Vaccine (Live Influenza Vaccine I and Live Influenza Vaccine II respectively). The vaccines were produced by the Irkutsk Federal State Unitary Company for the production of Immuno-Biological preparations. The strains which formed both vaccines were identified and prepared on a base of the current epidemical influenza viruses A/Peking/262/95 (HINI), A/Sydney/5/97 (H3N2) and B/St-Petersburg/95/20. The biological activity of each strain was not less than 10 6.5 EID50/0.2 ml for the influenza viruses type A and 10 6.0 EID50/0.2 ml for the influenza type B. The vaccine and placebo (allantoid fluid) were administered intranasally, using the 'RDZH-M4' sprayer 0.25 ml in each nostril. The Live Influenza Vaccine I was administered twice with an interval of 21 days and the Live Influenza Vaccine II was administered once
Outcomes	Effectiveness Influenza: "In order to carry out the serological correction of the clinical diagnosis, we tested 58 pairs of serum samples from those school children who had contracted influenza and acute respiratory illnesses in the inoculated and control groups. In 22 individuals, the diagnosis of influenza was confirmed serologically. Out of the 22, 18 (81.8%) individuals were from the control groups, 3 (13.6%) individuals had been inoculated twice with the Live Influenza Vaccine I, and 1 (4.6%) individual had been inoculated with the Live Influenza Vaccine II (for both the Live Influenza Vaccine I and the Live Influenza Vaccine II, $P < 0.001$)." This sentence does not make it clear whether there only 58 children who reported sick or how the sample was chosen and why a separate group of children had to be recruited to test serological responses Safety ARIs and allergic reactions. Harms' follow-up was 7 days
Funding Source	Government
Notes	The authors conclude that "during the period of the maximum rise of morbidity, the coefficient of efficacy for those inoculated twice with the Live Influenza Vaccine I was 48.8%. For those inoculated with the Live Influenza Vaccine II, the figure was 44.6% ($P < 0.05$)." However for influenza it was 83%. "Thus, both vaccines were highly effective. Moreover, the figures of efficacy for both preparations rose significantly after the serological correction of diagnoses". Possibly biased subset of influenza cases in follow-up . Means of selection of them and of children to assess antibody responses not described

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient descriptions
Allocation concealment (selection bias)	Unclear risk	Insufficient descriptions
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinding

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aa Grigor'eva 2002 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	High risk	No description
Summary assessments	Unclear risk	Plausible bias that raises some doubt about the results

aa Gruber 1990

Methods	Multicentre, randomised, placebo-controlled clinical trial to state effectiveness and safety of cold bivalent cold recombinant (CD) and trivalent inactivated (TIV) influenza vaccines. Randomisation and allocation procedure were not described
Participants	"One hundred ninety one (191) healthy children aged 3 to 18 years from 92 families recruited from HFS, Oklahoma Family Practice Center (Oklahoma City), Baylor College of Medicine Family Practice Clinic (Houston, Texas) were enrolled. Recruited families were independently randomised at each participating institution to form 1 of three immunisation groups: 30% were assigned to each vaccine group and 40% to the placebo group. Placebo recipients were randomly assigned to receive intranasal buffered saline or intramuscular sterile saline. No significant differences were noted in socioeconomic status, average size of the family, age distribution of the vaccine recipients. Thirty families were assigned to the TIV group (54 children), 25 to the CR group (58 children) and 37 to the placebo (77). UV family contacts were also followed up during the epidemic of B/Ann Arbor/86 (TIV =56 ; CR = 47 ; placebo = 72)"
Interventions	• Bivalent CR influenza A vaccine (CR) composed of 2 vaccine strains each of which contain the six genes coding for the cold-adapted parent influenza strain A/Ann Arbor/6/60. CR - 59 (H3N2, lot E-204, containing 107.3 TCID50 per ml) were diluted 1:10 with CR - 64 (H1N1, lot E - 221, containing 106.3 TCID50 per ml). CR - 64 and CR - 59 contain the hemagglutinin and neuraminidase of A/Dunedin/6/83 (H1N1) and A/Korea/1/82 (H3N2). 1 dose of 0.5 ml intranasally administered. • Trivalent inactivated influenza vaccine (TIV, Fluogen, subvirion, Parke Davis, Morris Plains, NJ) containing 15 mg of each A/Chile/83 (H1N1), A/Philippines/82 (H3N2), B/USSR/83 hemagglutinin antigens in 0.5 ml. 1 dose of 0.5 ml intramuscularly administered • Placebo consisting of either 0.5 ml of buffered saline (intranasally) or 0.5 ml of sterile saline (intramuscularly)
Outcomes	Serological Antibody titres Effectiveness • "Febrile Illness (including upper respiratory tract illnesses with fever, otitis media, influenza-like illnesses with fever, lower respiratory tract illnesses with fever) • Afebrile Illnesses (no definition given) • Influenza B infection When ongoing community surveillance at the Influenza Research Center (Baylor College of Medicine) indicated that influenza virus was present in the community, weekly telephone contacts to families were initiated to evaluate all respiratory illnesses. Home or clinic visits were scheduled for physical examination and collection of nasal washes

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	and throat swab specimens for virus isolation. Children and their families were followed up during the influenza B/Ann Arbor/86 epidemic (winter 85 - 86). An illness was attributed to influenza B infection if an isolate was obtained during the illness or, in a person with a postseason antibody rise only, if the illness occurred within 10 days of an isolate in household contact or during the period of most intensive viral activity in the community" Safety Families were contacted by telephone to record local, systemic, respiratory symptoms occurring within 2 weeks after vaccination
Funding Source	Government
Notes	"The authors conclude that TIV is highly effective but serological responses to CA vaccine depended on previous exposure and immunological memory 1. No precise information concerning the time the study was conducted 2. For the CR group efficacy data are not in the table. 3. Number of virus positive is not utilisable for the analysis 4. It is impossible to state how many participants received placebo intranasally and how many received it intramuscularly. This doesn't permit an analysis of the safety outcomes. There appears to be a major problem with this study. Randomisation and allocation are not described in detail, so the success of randomisation is unclear. In addition there is very long and detailed discussion on differences in susceptibility, exposure and immunological memory between arms of the trial, where CR recipients had lower serological responses to the circulating B/Ann Arbor strain. If this trial was randomised there should be no significant differences in immunological memory between participants"

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Insufficient descriptions
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient descriptions
Summary assessments	Unclear risk	Randomisation and allocation are not described in detail, so the success of randomisation is unclear

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ab Gruber 1996

Methods	Multicentre, randomised, double-blind, placebo-controlled clinical trial to assess the efficacy and safety of live attenuated, cold adapted influenza vaccine in children aged 6 to 18 months. Vaccine was administered either as monovalent or bivalent preparation in a randomised, double-blind manner (any description, author contact is needed)
Participants	Children aged 6 to 18 months who were enrolled at some vaccination units: Baylor College of Medicine, St. Louis University, University of Rochester, Vanderbilt University, University of Maryland. 182 participants were vaccinated, all were born after the last influenza A epidemic and had little opportunity for H3N2 exposure
Interventions	Monovalent live attenuated, cold adapted influenza vaccine A/Kawasaki/9/86 (H1N1) CR - 125, lot BDS 911501, 106.2 TCID50 per 0.5 ml in egg allantoic fluid • Monovalent live attenuated, cold adapted influenza vaccine A/Los Angeles/2/87 (H3N2) CR - 149, lot BDS 915301, 106.2 TCID50 per 0.5 ml in egg allantoic fluid • Bivalent live attenuated, cold adapted influenza vaccine A/Kawasaki/9/86 and A/Los Angeles/2/87 , lot BDS 915501, containing 106.2 TCID50 of each strains in 0.5 ml of egg allantoic fluid • Placebo consisting in egg allantoic fluid Vaccines were prepared by Wyeth-Ayerst (Philadelphia) Vaccine and placebo were administered as nose drops as 0.5 ml dose in the autumn of 1991
Outcomes	Serological HAI and ELISA were determined against H1N1 and H3N2 Effectiveness Subjects were monitored during the winter 1991-92 to evaluate the protection against influenza A H3N2 (A/Beijing/89) epidemic. Once influenza was detected by community surveillance, all participants were followed closely by weekly phone calls. A home visit was done if a subject had symptoms of respiratory illnesses or any household contacts had fever > 37.8°C and upper respiratory symptoms. In these cases a nasal wash for viral culture was obtained. Respiratory illnesses were classified as febrile or afebrile. Individual doing examination remained blinded to the treatment group. OM was coded separately. A total of 128 illnesses among 181 participants were identified. More than 50% of children with respiratory illnesses had viruses other than influenza. Influenza A/Beijing/89 was isolated from 23 children with respiratory illnesses Safety During the 10 days after vaccination, parents and guardians recorded the subject's temperature twice a day (morning and evening) and symptoms including cough, rhinorrhoea, diarrhoea (evening) once a day. Fever was considered any temperature > 37.8°C. For the other symptoms were considered at least 3 stools in 24 hours. Parents had to contact the study site if a subject had more than 1 symptom on a given day or had fever > 37.8°C. These were clinically evaluated. Diary information was unavailable for 2 children"
Funding Source	Government/industry
Notes	The authors conclude that live attenuated vaccines were significantly more effective than inactivated vaccines. Data about epidemic strain isolation in the 4 arms were pooled based on whether participants received a H3N2-containing vaccine or not. It is not possible to go back to the isolation in the single 4 arms

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ab Gruber 1996 (*Continued*)

Risk of bias		*Risk of bias*
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No description
Allocation concealment (selection bias)	Unclear risk	No description
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No description
Summary assessments	Unclear risk	Plausible bias that raises some doubt about the results

ab Gruber 1997

Methods	RCT, double-blind, multicentre to assess reactogenicity and safety of a cold adapted bivalent influenza vaccine containing the strains A/Kawasaki/9/86 (H1N1) virus and ca A/Beijing/352/89 (H3N2)
Participants	1126 children aged 2 to 36 months enrolled from 13 participating institutes in autumn 1993. Subjects were excluded if they had received any vaccine within 3 weeks before vaccination with influenza or placebo
Interventions	• Enrolled participants were randomised to receive 1 0.5 ml dose of cold adapted bivalent flu vaccine containing 104, 106 or 107 TCDI50 ca A/Kawasaki/9/86 (H1N1) virus and ca A/Beijing/352/89 (H3N2) virus per 0.5 ml dose or placebo, consisting of egg allantoic fluid • Vaccines and placebo were intranasal administered
Outcomes	Serological HAI titre against A/Kawasaki/9/86 and A/Beijing/352/89 were determined. Serum specimens were collected before vaccination and 35 days after by finger stick or venipuncture Effectiveness Not assessed Safety A diary card was kept by parent for seven days after immunisation. Temperature (recorded axillary, rectal or orally) and other symptoms were reported. Fever was considered as temperature 38.6°C rectal; 38.1°C orally or 37.5°C axillary
Funding Source	Government/Industry

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ab Gruber 1997 (*Continued*)

Notes	The authors conclude that CA vaccine is well tolerated and immunogenic but less so in very young children: The number of individuals in each study arm, is not clearly reported. Data from the table of respiratory symptoms (table 2 of this paper) do not agree with those reported in table 1 (fever). A total of 1126 study participants were enrolled but they resulted in 1249 from table 1 (and 1123 from table 2)

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No description
Allocation concealment (selection bias)	Unclear risk	No description
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Few losses to follow-up, unlikely to be related to true outcome
Summary assessments	High risk	Follow-up very short (7 days after each dose). Major denominator discrepancies between text and tables

ab Gutman 1977

Methods	Placebo-controlled clinical trial to asses safety and reactogenicity of monovalent A/New Jersey/8/76 administered as whole virus or split-product (disrupted virion) vaccine in four different preparation from licensed manufacturers
Participants	Children aged 3 to 10 years appeared at the Lincoln Community Health Center (LCHC, Durham, North Carolina) between May 24th and May 28th 1976, whose physicians allowed participation to the trial. Children were divided in two age groups (3 to 6 years and 6 to 10 years) and assigned to the preparation by continuous rotation of the vial numbers
Interventions	All vaccines were prepared from virus strain A/New Jersey/76 (Hsw1N1). Employed preparations were: • MN 100, MN 200 ; MN 400 (Merrell -National Laboratories, Cincinnati, Ohio) . Whole virus vaccine containing respectively 100, 200 or 400, chick cell-agglutination units) • MSD 100 (Merck Sharp & Dohme, West Point, Pa). Whole virus vaccine cont. 100 CCA units • W 100, W 200, W 400 (Wyet Laboratories, Philadelphia, PA). Split product vaccine cont 100, 200, 400 CCA units • PD 100, PD 200, PD 400 (Parke, Davis and Company, Detroit, Michigan). Split

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ab Gutman 1977 (*Continued*)

	product vaccine cont. 100, 200 or 400 CCA units • Placebo were also prepared by the same manufacturers as the vaccines. No information about composition given • Vaccines and placebos were administered in the deltoid muscle as single dose of 0. 25 ml
Outcomes	Serological 3 weeks after vaccination, a serum sample was taken to determine the antibody titre HAI to A/Victoria/3/75, A/swine/1976/31; A/Mayo Clinic / 103 /74 and A/ New Jersey/ 76 viruses. Children with titre above 1:20 to A/New Jersey were offered additional vaccination with MN 100 vaccine Effectiveness N/A Safety After immunisation children were observed at the LCHC for 20 minutes. Mothers were provided with 2 thermometers to record temperatures 6 and 9 hours later. Both were returned on the next day to be read by investigators. On the day after, children returned to be examined for adverse reactions or fever. Mothers recorded on a sheet adverse reactions (pain at the injection site, malaise, myalgia, headache, fever, nausea and tenderness, redness, induration). Sheets were completed the day after immunisation at the LCHC. During the study a physician was available when an adverse reaction was recognised or suspected by the parents
Funding Source	Government
Notes	The authors conclude that reactogenicity of both types of vaccines were similar. It is not clear if assignation to the vaccine or placebo group was made separately for the 2 age groups. Safety data are expressed considering only the vaccine group type (i.e. Split or whole virus) and not each arm , that was effectively randomised. The placebo arm is reported in an aggregate fashion with no age breakdown, making vaccine comparison impossible

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not used
Allocation concealment (selection bias)	Unclear risk	No descriptions
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses

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ab Gutman 1977 (*Continued*)

Summary assessments	Unclear risk	It is not clear if assignation to the vaccine or placebo group was made separately for the 2 age groups

ba Hirota 1992

Methods	Case-control study to asses correlation between ILIs and influenza immunisation status in schoolchildren aged between 6 and 12 years during an epidemic
Participants	814 children from 1 of the 9 elementary schools of Kasuga City (Fukoka Prefecture, Japan). Children were aged 6 to 12 years
Interventions	Immunisation with commercial inactivated flu vaccine prepared with the strains A/Yamagata/120/86 (H1N1), A/Fukoka/C29/85 (H3N2), B/Nagasaki/1/87. Each ml of vaccine contained 200 CCA units of each strains. Vaccine was subcutaneously administered in 2 doses of 0.3 ml. Vaccination was carried out after consensus from parents was obtained: the first dose was administered on October 25th while the second on November 16th, 1988. 496 children (60.9%) were not immunised, 187 (23.0%) received 2 doses of vaccine and 131 (16.1%) only 1 dose From data recorded by the Surveillance System for Tuberculosis and Infectious Diseases, an influenza epidemic lasted in Fukoka between October 30th and April 1st (with a sharp peak between December 25th and February 11th), which was caused mainly by the strains A H1N1 (95%), A/H3N2 (3%) and B (2%. Percentages refer to 1575 isolates from all Japan)
Outcomes	Serological N/A Effectiveness • "Symptoms of acute respiratory illnesses (ARI): fever (< 37°C, 37°C to 40°C by 0.5°C intervals), rhinorrhoea, cough, sore throat, nausea or vomiting, diarrhoea, abdominal pain • Actions taken due to the symptoms: taking medicine, seeking doctor's consultation, school absenteeism • Gestational age • Predisposition: easily inflamed tonsils, liable to get eczema, precedent asthma, allergies • Usual dietary intake, gargling, physical exercise, sleeping hours, family composition, passive smoking, numbers of rooms, total room space, window or door sashes, home heating Cases were defined as: • MILI (mild influenza-like illnesses): all individuals with fever 38°C < 39°C, with absenteeism and medical consultation • SILI (severe influenza-like illnesses): individuals with fever 39°C with absenteeism and medical consultation Controls defined as: • NS (no-symptoms group). All those participants with no ARI onset, no absenteeism, no medical consultation during the same period (January 8th - February 11th 1989) Questionnaires were returned from the parents of 803 children. MILI and SILI groups were composed from 48 and 80 children respectively. Control group NS consisted of 196 children" Safety N/A
Funding Source	Unclear

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ba Hirota 1992 (*Continued*)

Notes	"The authors conclude that vaccination was effective against SILI but not MILI-case definition omits ARI onsets during the first 2 weeks of epidemic peak and those after the period (enhances it for the conservative determination for the risk factor). Immunisation data for MILI were not shown. Criteria for selection of case and controls (i.e. absenteeism and medical consultation) might have introduced selection bias"

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
CC-Case Selection	Unclear risk	Based on self-report
CC-Control Selection	Unclear risk	Not independent from case selection
CC-Comparability	High risk	No description
CC-Exposure	Low risk	Secure record
Summary assessments	High risk	Vaccination was voluntary but its basis was not described

aa Hoberman 2003a

Methods	RCT to assess effectiveness of inactivated influenza vaccine against OM and influenza. 2 groups in 2 following years were randomised before beginning of the respiratory season (December 1st to March 31 of each year) to receive 2 doses of vaccine or placebo
Participants	Children aged 6 to 24 months enrolled at Children Hospital of Pittsburgh. In the first study year 417 children were enrolled and randomised between October 4th and November 30th, 1999) to receive 2 doses of vaccine or placebo. In the second study year 376 children were randomised between September 5th and December 8th, 2000)
Interventions	• Participants were stratified according to whether they were prone to OM (at least 3 episodes occurred in the last 6 months or 4 in the last year) • In the second study year participants were also stratified depending if they received at least 1 dose of pneumococcal conjugate vaccine • Within each stratum children were randomised in blocks of 9 by means of a computer-generated list to receive 2 doses of vaccine or placebo in ratio 2:1. The 2 doses were intramuscularly administered approximately 4 weeks apart First study year: • Inactivated trivalent subvirion influenza vaccine (Fluzone, Aventis Pasteur, Swiftwater, Pa) containing strains A/Beijing/262/95 (H1N1) , A/Sydney/15/97 (H3N2), B/Yamanashi/166/98 versus • Placebo consisting of a standard diluent and supplied also by Aventis In both years 2 doses were administered 4 weeks apart Of the 417 initial participants, 278 were randomised to receive placebo and 139 to

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	placebo. Five participants in the vaccine and 1 in the placebo group were discarded because of failure to meet eligibility criteria. The first dose was administered to 273 (vaccine) and 138 (placebo) children. The second dose was administered to 267 and 134 participants respectively Second study year: • Inactivated trivalent subvirion influenza vaccine (Fluzone, Aventis Pasteur, Swiftwater, Pa) containing strains A/New Caledonia/20/99 (H1N1), A/Panama/2007/99 (H3N2), B/Yamanashi/166/98 versus • Placebo (standard diluent, Aventis) 1 subject from the placebo group was excluded for failure to reach eligibility. 252 children were administered vaccine, 123 placebo. The second dose was administered to 246 and 118 participants respectively
Outcomes	Serological • Seroconversion. 4-fold increase in antibody titres or post-immunisation titre > 1:40 (before immunisation/4 weeks second dose) Effectiveness "First study year: Biweekly visit carried out after the second dose of vaccine up to 31 March 2000 (4 months); Monthly visits up to November 15th, 2000 Second study year: Biweekly visits from after second dose was administered (December 2000) up to March 31st, 2001 (4 months) Parents were instructed to contact staff for cases of upper respiratory tract infection or otitis. In these cases an interim visit was conducted • Acute care visits: visits resulted from fever (38°C) within 72 hours or occurrence of otalgia or illness-related visit to the primary care clinicians • Middle ear effusion: decreased or absent tympanic membrane mobility; yellow or white discolouration of the tympanic membrane; opacification of tympanic membrane not due to scarring; visible bubbles or air-fluid levels. Outcome is defined as presence of at least 2 symptoms • Acute otitis media: presence of purulent otorrhoea of recent onset not due to otitis externa or middle ear effusion accompanied by 1 or more symptoms: ear pain, marked redness of the tympanic membrane, bulging of the tympanic membrane • Influenza: positive culture obtained from throat swab during visits at which study participants had upper respiratory tract infection accompanied by fever (38°C) or acute otitis media or both (during flu seasons: first year Jan 3rd-Feb 15th, 2000; second year Jan 4th-March 30th, 2001) In the first study year 25 cases occurred during the epidemic and a further 12 in the following 25 weeks of surveillance. In the second study year the corresponding values were 11 and 2 (sixteen weeks surveillance)" Safety • "Minor systemic or local adverse events were not systematically recorded (1 child had 2 brief episodes of unexplained staring on the day of the first vaccination; 1 had mild intercostals reactions and wheezing 1 day after the second vaccination; 1 child developed acute gastroenteritis 3 days after first vaccination) • Other possible adverse were monitored during the care visits"
Funding Source	Industry

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aa Hoberman 2003a (*Continued*)

Notes	The authors conclude that the vaccine was well tolerated but had no effect on OM, resource consumption, or any of the other indicators

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number, computer-generated list, block randomisation (block of 9)
Allocation concealment (selection bias)	Low risk	"randomisation lists were kept in locked files not accessible to blinded personnel"
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate
Summary assessments	Low risk	Plausible bias unlikely to seriously alter the results

aa Hoberman 2003b

Methods	See aa Hoberman 2003a
Participants	
Interventions	
Outcomes	
Funding Source	
Notes	

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number, computer-generated list, block randomisation (block of 9)
Allocation concealment (selection bias)	Low risk	"Randomisation lists were kept in locked files not accessible to blinded personnel"

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aa Hoberman 2003b (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate
Summary assessments	Low risk	

ca Jianping 1999

Methods	Cohort study carried out on people from the Chinese Peoples' Liberation Army (PLA) between December 1996 and May 1997
Participants	"One hundred and sixty-eight children aged 3 to 6 years from the PLA in areas not considered at risk and who had not had influenza recently (adult and elderly data not extracted). Vaccinated groups consisted of 80 children aged between 3 and 6 years, 363 adults between 18 and 59 and 235 elderly over 60 years Controls were not immunised. Correspondent groups consisted respectively of 88 (children), 372 (adults) and 218 (elderly) people"
Interventions	Inactivated influenza vaccine "Vaxigrip" (Pasteur Mérieux Connaught, France). Children up to 3 years were immunised with 2 doses of 0.25 ml administered 1 month apart. A single dose of 0.5 ml was administered to children over 3 years and adults
Outcomes	Serological N/A Effectiveness "All participants were observed from 21 days to 6 months after vaccination. They were asked to report the following symptoms: fever over 38.5°C, headache, myalgia or arthralgia, cough, sore throat and coryza. Cases of fever for other causes were excluded • Influenza-like syndrome: presence of fever over 38.5°C and headache, myalgia or arthralgia • Common cold: associated with 1 of the following: fever, headache, myalgia or arthralgia, cough, rhinorrhoea, sore throat • Upper respiratory tract symptoms: influenza-like syndrome + common cold" Safety Not assessed. Only serious adverse reactions that occurred during the study are reported
Funding Source	Government
Notes	"The examined vaccine was strongly protective in populations of different ages • The difference between outcomes is unclear. Gender was not considered in the reporting and it appears strange that children are enrolled in the PLA • May have lost a lot in translation. Very confusing outcome definition and overlap. We have a problem believing that the vaccine protected from the common cold. Viral circulation was not discussed"

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ca Jianping 1999 (*Continued*)

Risk of bias		*Risk of bias*
Bias	**Authors' judgement**	**Support for judgement**
PCS/RCS-Selection Exposed cohort	Unclear risk	Insufficient description
PCS/RCS-Selection Non Exposed cohort	Unclear risk	Insufficient description
PCS/RCS-Comparability	Unclear risk	Insufficient description
PCS/RCS-Assessment of Oucome	High risk	Self-reported
Summary assessments	High risk	Plausible bias that seriously weakens confidence in the results

ca Kawai 2003

Methods	Prospective cohort study carried out during 2001 to 2002 in 38 practices in Japan (staffed by participating members of the Japanese Physicians Association. Doctors enrolled consenting vaccinated participants on an Internet-based register from 1 October to 31 December, 2001. UV participants were selected by the researchers from the same clinic and matched by age and sex. By 31 May, 2002 researchers added data on symptoms of ILI and AE experienced by the participants. Information was elicited on the basis of self reported questionnaires, emails or phone calls
Participants	Children aged 0 to 15 years (older children participated but from 16 years are not separable from 16 to 64 years age group), adults and elderly up to the age of 104. In total 8841 participants took part in the cohort study
Interventions	Inactivated influenza vaccine containing A/New Calendonia/20/99 + A/Panama/2007/99 + B/Johannesburg/5/99 once or twice. History of previous year's exposure was also elicited. A sliding scale of doses was used for age groups. Results are presented by 1, 2 or no immunisations
Outcomes	Serological Rapid kit testing was carried out in 75 of the 124 participants with ILI symptoms and 64 of these were positive (A viruses recovered from 3 of them). Paired sera were positive in 5 of the 6 participants in whom they were taken Effectiveness ILI (sudden onset, temperature over 38C, sore throat and fatigue). Influenza was defined as ILI plus rapid test diagnosis, or serum antibody increase or viral isolation Safety Data for 96 participants are reported for the vaccinated arm but not for those in the UV arm
Funding Source	Istitutional

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Notes	The authors conclude that the vaccines were 67.6% and 84.5% effective respectively against ILI (1 or 2 immunisations) and 54% and 79.8% against influenza (1 or 2 immunisations). No protection against ILI was conferred by immunisation the previous season. Despite an extensive baseline description of the three arms the study has so many problems that the results are difficult to interpret: selection of participants, practices and controls, lack of specification of viral circulation and matching, non-random serological testing, loss of safety data. Particularly non-random kit testing makes a nonsense of the conclusions of the study. It is very strange that 64/8841 had influenza and yet had 84% efficacy

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
PCS/RCS-Selection Exposed cohort	Unclear risk	Volunteer, non-information on number of doses
PCS/RCS-Selection Non Exposed cohort	Unclear risk	Volunteer
PCS/RCS-Comparability	Unclear risk	Matching by clinic age sex
PCS/RCS-Assessment of Oucome	High risk	No information on follow-up length, self-reported
Summary assessments	High risk	Despite an extensive baseline description of the three arms the study has so many problems that the results are difficult to interpret: selection of participants, practices and controls, lack of specification of viral circulation and matching

aa Khan 1996

Methods	Single-blind, placebo-controlled randomised trial to compare the efficacy of trivalent cold adapted and trivalent inactivated split-virus influenza vaccine. During the period 1 Jan to 2 Feb, 1992 there was a local epidemic of A/H3N2 (no better defined)
Participants	Children aged 9 to 12 years from 2 schools of Vologda (USSR). Participants were excluded if they had an acute illness, oral herpetic lesions, temperature > 37.0°C on the day of inoculation or a history of egg allergy or severe reaction to previous influenza vaccination. A total of 555 children were enrolled between 21 October and 1 November, 1991. 245 were enrolled from the school 1 and 310 from the other school
Interventions	After a physical examination participants were randomly assigned to receive vaccine or placebo, using the route of administration previously chosen by parents or guardians. For this purpose a blocked randomisation scheme was used with a vaccine to placebo ratio of 2:1 Vaccines

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	• Trivalent, live attenuated, cold adapted influenza vaccine (produced by Odessa Production Company for Biological Products, Odessa, Ukraine), was made using the donor strains A/Leningrad/134/17/57 H2N2 and B/Leningrad/14/55. The wild type viruses used were A/Leningrad/92/89 H1N1, A/Zakarpatje/354/89 H3N2 and B/Yagamata/16/88. Live vaccine contained 7.0 to 7.5 log10 EID50 of each virus per 0.5 ml dose (200). A single 0.5 ml dose was administered intranasally. Egg allantoic fluid as placebo (100) • Commercial trivalent inactivated split-virus influenza vaccine (Wyeth-Ayerst, Philadelphia) containing 15 μg of haemagglutinin of A/Taiwan/1/86 H1N1, A/Shanghai/16/89 H3N2 and B/Yamagata/16/88 1990 to 91 formulation). (168) The vaccine was administered as a single 0.5 ml dose injected into the deltoid muscle with disposable, unit dose syringe and needle • Saline solution as placebo (87) The vaccine groups do not differ significantly by age, sex, school, grade attended, or seronegativity for the 3 strains. Blood specimens were collected by fingerstick on the day of inoculation and again 28 days and 5 months after inoculation
Outcomes	Serological Three sera samples over the period of 5 months were taken from about half the children Effectiveness Schoolchildren absent for medical reasons were examined from physician who was not affiliated with the study and re-examined before they return to school. A letter stating the medical condition causing their absence was filled out. These data were recorded onto the child's school medical card and covered the period 10 November 1991 to 17 March 1992, were transcribed from the medical card at the time of serum collection 5 months after vaccination. Absenteeism due to ILI was defined as the first school absence with physician's diagnosis of either acute respiratory disease or influenza. The epidemic lasted from 1.1. to 2.2.1992. (Specific diagnosis of influenza refers to an acute respiratory illness occurring during the official influenza season and is a clinical diagnosis, moreover the employed criteria were not uniform and these outcomes were not used). Vaccine efficacy was also estimated by using 4-fold serum antibody increase to A H3N2 (circulating virus) Safety Children enrolled during the first week were monitored daily for 4 days after inoculation. Those enrolled during the second week were monitored on the day after inoculation. Children with reaction after inoculation were monitored by paediatricians who were unaware of the child's vaccine group until the symptoms resolved. Data on low grade axillary fever and other local reactions were reported. Some harms are reported with insufficient information for extraction (coryza and sore throat)
Funding Source	Government
Notes	The authors conclude that there is no significant difference between live attenuated and inactivated vaccine in preventing school absence due to ILI but both are significantly more effective than placebo. The authors report ILI and assume it to be influenza because of the background rate. The text is also contradictory because half the participants are supposed to have had serology carried out on a non-random basis but the middle line of Table 2 (reporting more than 4-fold titre rise) appears to indicate that school absentees had titres done and lumps absences with titre rises under "both" with a calculation of vaccine efficacy. The 2 placebos are not reported separately, so it is impossible to assess

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aa Khan 1996 (*Continued*)

	safety apart from what is in the text at page 173 right hand column. Denominators do not match between tables and text and the only mention of attrition is the statement that medical card for 5 of the 555 participants were not received

Risk of bias		***Risk of bias***
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient descriptions
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Single
Incomplete outcome data (attrition bias) All outcomes	Low risk	Few losses to follow-up
Summary assessments	Unclear risk	Possible confounding by indication

ab King 1998

Methods	Randomised, placebo-controlled, multicentre trial
Participants	Children aged 18 to 71 months in good health. 238 were altogether enrolled at Baylor College of Medicine Houston, Cincinnati Children Hospital, Saint Louis University and University of Maryland at Baltimore in three steps. 118 were enrolled from one ambulatory clinic in the northern area of Santiago (Chile)
Interventions	Cold adapted trivalent flu vaccine containing the strains A/Johannesburg/33/94 (H3N2) , B/Panama/45/90 and A/Texas/36/91 (H1N1) in different titre (10^4, 10^5, 10^6 or 10^7 $TCID_{50}$ of each strain) versus placebo Vaccine and placebo (allantoic fluid) were assigned in double-blind manner using a randomisation table provided by the manufacturer (Avion). Enrollment took place in 3 steps : • 115 children in the USA and 60 in Chile were randomised to receiver either 10^4 or 10^5 TCID50 of vaccine or placebo at a ratio of 1:1:1 • 59 children in the USA and 30 in Chile were randomised to receive 10^6 $TCID_{50}$ of vaccine or placebo at 2:1 ratio • 64 children in the USA and 28 in Chile were randomised to10^7 $TCID_{50}$ of vaccine or placebo in a 2:1 ratio In the USA the randomisation was designed so that 50% of the participants received vaccine or placebo as drops and the remaining 50% by spray

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ab King 1998 (*Continued*)

Outcomes	Serological Antibody titres Effectiveness N/A Safety Temperature was recorded each evening within 10 days after vaccination on a diary card. Other daily recorded symptoms were: cough, wheezing, rhinorrhoea, sore throat, or irritability. Children were examined by clinicians if an axillary, oral or rectal temperature > 38°C was observed
Funding Source	Government/Industry
Notes	The authors conclude that the vaccine was safe and immunogenic in 2 of the 3 strains. Small denominator

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient descriptions
Allocation concealment (selection bias)	Unclear risk	No description
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Insufficient descriptions
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up
Summary assessments	Unclear risk	Insufficient information about study design

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ca King 2006

Methods	Prospective cohort study carried out at 24 public elementary schools in Maryland, Texas and Minnesota and 4 (kindergarten to elementary) in Washington during 2004-2005. The study aimed at assessing the effect of a school based vaccination programme on the households of children attenders. The schools were divided into 11 clusters, 7 of which had random selection of the intervention school and the other 4 were selected in a non-random way. The remaining schools were controls. Clusters were matched by geographic, ethnic and social class variables. There was a peak circulation period of influenza around the end of January 2005. Other household members could have been also vaccinated. After the peak week all households who had children in study schools received an anonymised questionnaire. The text also refers to a post hoc analysis of vaccinated and non-vaccinated children regardless of school. This appears to be a second study and also appears to imply that some of the "control school children" (as well as the household members) were vaccinated
Participants	5840 pupils in intervention schools and 9451 in control schools, mainly whites in both arms
Interventions	Live attenuated vaccine (Medimmune) intranasally (no better defined) to all children aged 5 or more or do-nothing. Content of the vaccine was that of the 2004 to 2005 season. The paper describes main circulating virus (A/California/7/2004 H3N2) as drifted from the strain in the vaccine (not described)
Outcomes	Effectiveness ILI, School absenteeism, serious harms at 42 days after vaccination Safety Reported in an appendix
Funding Source	Industry
Notes	The authors conclude that "Most outcomes related to influenza-like illness were significantly lower in intervention-school households than in control-school households. (ClinicalTrials.gov number, NCT00192218.)". There are several descriptions of the 2005 peak influenza period but there is no information on vaccine content although matching must have been at least incomplete as the text described a drifted circulating variant. There is no clear description of age of children or households, of vaccines, of very major discrepancies in denominators of the possible impact of bias of schools who refused to be controls and refused originally proposed placebos. How did this study achieve a trial registration number? It must be an aborted trial

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
PCS/RCS-Selection Exposed cohort	Unclear risk	Insufficient descriptions
PCS/RCS-Selection Non Exposed cohort	High risk	No description
PCS/RCS-Comparability	High risk	Insufficient information

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ca King 2006 (*Continued*)

PCS/RCS-Assessment of Oucome	Unclear risk	Self-report
Summary assessments	High risk	There is no clear description of age of children or households, of vaccines, of very major discrepancies in denominators of the possible impact of bias of schools who refused to be controls and refused originally proposed placebos

ab Levine 1977

Methods	Double-blind placebo-controlled phase 1 randomised trial carried out in the summer of 1976 in Baltimore, USA. The aim was to compare reactogenicity and safety of various concentrations of whole-virion vaccines with split products of various manufactures
Participants	158 Maryland children aged 3 to 5 years. 103 children took part in the 1-dose evaluation of split products, 47 took part in the 1-dose evaluation of whole virion products and 28 took part in the 2-dose evaluation of whole virion products
Interventions	50, 100 and 200 CCA units of split vaccines (Parke Davis or Wyeth) or 50 or 100 CCA units of whole-virion vaccines (MSD or Merrell) or placebo. All vaccines were monovalent containing A/New Jersey/8/76 (H1N1). All were administered as single doses except for a follow-up of second doses only for whole-virion vaccines. Discontinuation of the use of split vaccines was caused by the disappointing antibody responses
Outcomes	Serological Paired sera for antibody titres Effectiveness N/A Safety Fever, nausea and malaise and a reactogenicity score with definitions described in the Lerman 1977 study
Funding Source	Government
Notes	The authors conclude that both vaccines were generally well tolerated with whole-virion products causing low grade pyrexia and split products being virtually non-immunogenic in 1-dose schedules. A well described study

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient descriptions

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ab Levine 1977 (*Continued*)

Allocation concealment (selection bias)	Low risk	"preparations of vaccines and placebo in coded vials were supplied by the Bureau of Biologics"
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up
Summary assessments	Low risk	A well described study

ca Maeda 2002

Methods	Prospective open cohort study assessing the effects of TIV on children. The study took place in Japan between November 1999 and April 2000
Participants	Eighty-six healthy recipients of TIV and 94 aged-matched controls aged 5 to 83 months. Controls were randomly selected from hospital medical records of healthy infants. Age and sex of participants are described in Table 1. There is no mention of attrition and age and gender of participants appear evenly matched
Interventions	TIV containing 200 CCA/ml of A/Beijing/262/95(H1N1), 350 CCA/ml of A/Sydney/5/97 (H3N2) and 300 CCA/ml of B /Shandong/7/97. 2 injections were given subcutaneously 14 days apart. Dosage was on sliding scale per age: children < 1 year got 0.1 ml, those aged 1 to 6 years 0.2 ml and those > 6 years 0.3 ml. The comparator was do-nothing as placebo administration was not possible "for ethical reasons"
Outcomes	Serological Immunoassay (rapid test, Directigen FLU A, Becton Dickenson, USA), capable of detecting only influenza A Effectiveness Influenza A. Swabs were taken from children reporting to the hospital as instructed with a temperature > 37.8 C. Follow-up was from January to April 2000 Safety N/A
Funding Source	Unclear
Notes	The authors conclude that inactivated influenza vaccine reduces the incidence of influenza A virus infection in children aged 2 to 6 years but not in 6 to 24 months old (as 4 out of 5 inflected vaccinees belonged to this group). Selection bias may be at play as the enrolment procedure is not described and the study controls only for age and sex. In addition controls were selected on the basis of medical records which may mean that the controls had had a recent medical contact (although none of them had been vaccinated in the previous 12 months). Viral circulation and vaccine matching are not described

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ca Maeda 2002 (*Continued*)

Risk of bias		*Risk of bias*
Bias	**Authors' judgement**	**Support for judgement**
PCS/RCS-Selection Exposed cohort	Unclear risk	Insufficient description
PCS/RCS-Selection Non Exposed cohort	Unclear risk	Matched infants in good health
PCS/RCS-Comparability	Unclear risk	Matched infants
PCS/RCS-Assessment of Oucome	Unclear risk	Laboratory
Summary assessments	High risk	Selection bias may be at play as the enrolment procedure is not described and the study controls only for age and sex. In addition controls were selected on the basis of medical records which may mean that the controls had had a recent medical contact

ca Maeda 2004a

Methods	Prospective open cohort study of inactivated TIV over three seasons in Japan. Placebo was not used for ethical reasons. Children came to hospital if they developed febrile illness within 48 hours of inoculation. The follow-up period was from January to April each year
Participants	175 children were given vaccine every November or December of 1999, 2000 or 2001. For the control group 171 aged-matched children in good health who had not received influenza vaccine within 1 year of enrolment were randomly assigned from medical records of hospitals
Interventions	Inactivated vaccines for the three seasons: 1. 1999/2000 - A/Beijing/262/95 (H1N1) 200 CCA/ml*, A/Sydney/5/97 (H3N2) 350 CCA/ml* and B/Shandong/7/97 2. 2.2000/2001 - >15 µg hemagglutinin/0.5 ml A/New Caledonia/20/99 (H1N1), A/Panama/2007/99 and B/Yamanashi/166/98 3. 3.2001/2002 - >15µg hemagglutinin/0.5 ml A/New Caledonia/20/99 (H1N1), A/Panama/2007/99 and B/Johannesburg/5/99
Outcomes	Serological Influenza A virus infection determined using Becton Dickenson Directigen FLU-A antigen test performed according to direction of manufacturer. Test utilises enzyme-conjugated monoclonal antibodies Effectiveness Influenza A infection. If temperature > 38°C throat swab taken and tested for influenza A Safety N/A

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ca Maeda 2004a (*Continued*)

Funding Source	Government
Notes	The authors conclude that in small children below the age of 24 months the vaccine is not protective. The authors report that there were no complications and no hospitalisations

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
PCS/RCS-Selection Exposed cohort	Unclear risk	Insufficient description
PCS/RCS-Selection Non Exposed cohort	Unclear risk	Matched infants in good health
PCS/RCS-Comparability	Unclear risk	Matched infants
PCS/RCS-Assessment of Oucome	Unclear risk	Laboratory
Summary assessments	High risk	Selection bias may be at play as the enrolment procedure is not described

ca Maeda 2004b

Methods	See Maeda 2004a
Participants	
Interventions	
Outcomes	
Funding Source	
Notes	

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
PCS/RCS-Selection Exposed cohort	Unclear risk	Insufficient description
PCS/RCS-Selection Non Exposed cohort	Unclear risk	Matched infants in good health
PCS/RCS-Comparability	Unclear risk	Matched infants
PCS/RCS-Assessment of Oucome	Unclear risk	Laboratory

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ca Maeda 2004b (*Continued*)

Summary assessments	High risk	Selection bias may be at play as the enrolment procedure is not described

ca Maeda 2004c

Methods	See Maeda 2004a
Participants	
Interventions	
Outcomes	
Funding Source	
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
PCS/RCS-Selection Exposed cohort	Unclear risk	Insufficient description
PCS/RCS-Selection Non Exposed cohort	Unclear risk	Matched infants in good health
PCS/RCS-Comparability	Unclear risk	Matched infants
PCS/RCS-Assessment of Oucome	Unclear risk	Laboratory
Summary assessments	High risk	Selection bias may be at play as the enrolment procedure is not described

cb Nicholls 2004

Methods	Retrospective cohort study of an outbreak of influenza A(H3N2) between 10 March and 5 April 2002 in a semi-closed highly-vaccinated religious community in UK. 90% of members of the community had been vaccinated before 7 November 2001. Data collected by self-completion questionnaire, response rate was 92% (350/380)
Participants	350 residents of religious community including 133 children aged 0 to 14 years
Interventions	Inactivated trivalent influenza vaccine containing A/Moscow/10/99-like (H3N2), A/New Caledonia/20/99-like (H1N1) and B/Sichuan/379/99-like. The study reports a comparison of efficacy of the vaccine in members vaccinated in the US with those vaccinated in the UK, in effect testing the hypothesis of possible lower efficacy of the UK administered vaccine

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cb Nicholls 2004 (*Continued*)

Outcomes	Serological Throat swabs from 39 case volunteers, 10 non-cases and 5 of undefined status. Paired sera from 9 members and single sera from 2 were drawn. 27 throat swabs were positive for H3N2/Panama/2007/99-like, which is well matched to vaccine content Effectiveness A case was defined as self-reported fever or chills accompanied by 1 or more of cough, sore throat, headache. Outcomes were evaluated by questionnaires distributed on 2 April, 2002 Safety N/A
Funding Source	Unclear
Notes	The authors conclude that the vaccine was not effective in preventing the outbreak, despite being well matched to the circulating virus (risk of developing ILI symptoms was not significantly different between vaccinated and UV: OR 1.14, 95% CI 0.41 to 3.14). VE was -5% in those vaccinated in the UK and 77% (53.2% to 88.4%) for those vaccinated elsewhere, mainly in the US. The study reflects its mostly retrospective nature. The outbreak peaked on 20 March, 5 days before the arrival of the investigators. We do not understand why there is no matching of ILI cases with positive influenza diagnosis by vaccine exposure. Why report effectiveness when they could report efficacy?

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
PCS/RCS-Selection Exposed cohort	High risk	Selected cohort
PCS/RCS-Selection Non Exposed cohort	Unclear risk	Same community
PCS/RCS-Comparability	High risk	Insufficient information
PCS/RCS-Assessment of Oucome	High risk	Self-report
Summary assessments	High risk	Plausible bias that seriously weakens confidence in the results

ab Obrosova-Serova 1990

Methods	Randomised, blind, placebo-controlled trial to assess reactogenicity in children of live attenuated cold-adapted influenza B vaccine
Participants	"The study was conducted in a children's nursery and in a children's boarding school. 109 children and 87 children 3 to 15 years old received respectively vaccine or placebo"
Interventions	Enrolled participants were randomised to receive at least 1 dose or 2 doses of live attenuated cold-adapted influenza B vaccine derived by re-assortment between wild-type B/

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ab Obrosova-Serova 1990 (*Continued*)

	Ann Arbor/1/86 and ca B/Leningrad/14/55 viruses. First dose vaccine or placebo was administered at day 0 and second dose after 3 weeks. 0.5 ml vaccine or placebo were administered intranasally by aerosol spray. Placebo consisted of distilled water At the time of the study no evidence of circulation of influenza B viruses in Moscow was reported to the laboratory responsible for surveillance in the region
Outcomes	Serological HI titre against LEN-B/14/5/1 reassortant virus. Sera were collected by finger stick before the first and second inoculations and three weeks later. Estimation Effectiveness N/A Safety Adverse reactions were defined as fever (axillary temperature >37.5°C) and upper respiratory symptoms (coryza and/or pharyngitis) observed for four days after each inoculation
Funding Source	Government
Notes	• The authors conclude that the vaccine was immunogenic in younger children but less so in older children • There was lot of unexplained attrition between the first and second inoculations

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No description
Allocation concealment (selection bias)	Unclear risk	Not used
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Single-blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	There was lot of unexplained attrition between the first and second inoculations
Summary assessments	High risk	There was lot of unexplained attrition between the first and second inoculations

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ca Ozgur 2006

Methods	Single-blind prospective study carried out during the 2003 to 2004 season in children from 8 day care nurseries around Ankara, Turkey. The study aim was to assess the effectiveness of TIV in preventing AOM and OME. Randomisation is not mentioned, comparator is do-nothing and denominators are uneven. The single-blind design refers to the ear, nose and throat (ENT) tympanomtrist. The influenza period was defined as 15 Dec 2003 to 31 Jan 2004 on the basis of influenza and RSV isolates in the community. Three other influenza periods are also described
Participants	135 healthy daycare children aged 6 to 60 months. 16 children were excluded from the study (3 because of tympanostomy tubes, 11 because they could not complete the minimum of 3 follow-up visits and 3 because of failure to have the second vaccination). The authors report their analysis for 119 children (61 vaccinated and 58 UV, mean age 43 months). There were 22 children aged less than 2 years. The arms were similar for breast feeding, gender, dummy use, history of frequent URTIs, antibiotic use, allergy, asthma, previous OM and passive smoking
Interventions	TIV containing A/Moscow/10/99 (H3N2), A/New Caledonia/20/99 (H1N1) or B/Hong Kong/330/2001 in 2 doses (Fluarix or Vaxigrip). No mention is made of the circulating strains, although content of the vaccine was that recommended by WHO
Outcomes	Effectiveness OM diagnosed at tympanometry and otoscopy by a blinded ENT surgeon: normal ear (no abnormality and type A and C1 curves on tympanometry), AOM (hyperemia, opacity, bulging or immobility of the TM together with any of the following: fever, earache, irritability and vomiting), OME (retraction, opacity, bulging or immobility of the TM without clinical signs and with C2 or B tympanometry curve), OM (any episode of either AOM or OME)
Funding Source	Unclear
Notes	The authors conclude that "The frequencies of AOM, OME and total otitis media episodes in vaccinated children were 2.3%, 22.8% and 25.2%, respectively and these frequencies were 5.2%, 31.1% and 36.3% in the UV group. The difference was statistically significant ($P < 0.01$). This difference was especially prominent in the influenza season ($P < 0.05$). Influenza vaccine is effective in reducing AOM and OME episodes in 6- to 60-month-old day care children, especially during influenza season". The message is mixed as the authors point out that the relatively low effectiveness of TIV makes mass vaccination to prevent an OM (a syndrome) impractical. Not very detailed report, likely to be a cohort or CCT. Confusingly reported outcome data in Table 2. Numerators were extracted from the text

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
PCS/RCS-Selection Exposed cohort	Unclear risk	Insufficient description
PCS/RCS-Selection Non Exposed cohort	Unclear risk	Insufficient description

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ca Ozgur 2006 (*Continued*)

PCS/RCS-Comparability	High risk	Possibly confounding by indication
PCS/RCS-Assessment of Oucome	Unclear risk	Secure record
Summary assessments	High risk	Possibly companioning by indication

aa Principi 2003

Methods	Randomised controlled open trial assessing the socioeconomic impact of virosomal vaccine compared to no intervention. The trial is reported very briefly within a wider descriptive paper reporting incidence of influenza in a prospective cohort of 3771 children aged around 3.5 years reporting to ER or family paediatricians with ILI symptoms. The cohort has been excluded because of lack of exposure to vaccines and selected nature of participants
Participants	303 children; mean age 3.2 years, (range 6 months to 5 years)
Interventions	Virosomal intramuscular vaccine (Inflexal, Berna, no further details given) or no intervention
Outcomes	Serological N/A Effectiveness URI, febrile URTI, LRTI, drug px and days off school. Not otherwise defined, reported presumably as means and SD Safety N/A
Funding Source	Unclear
Notes	• The authors conclude that the findings support the wider use of influenza vaccine in healthy children of all ages to reduce the socioeconomic burden of influenza in the community • Brief reporting, randomisation, vaccine, circulation matching and outcomes are not described. CIs not reported, tables do not specify means and SD, the recommendations on "children of all ages" is at odds with the lack of breakdown of age groups. No funding source is reported. Published in supplement sponsored by? THE STUDY IS LINKED TO ESPOSITO 2006 WHICH PRESENTS THE SAME DATA

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described

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aa Principi 2003 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Possibly no losses
Summary assessments	Unclear risk	Insufficient information to assess study design

cb Ritzwoller 2005

Methods	• Retrospective cohort study of effectiveness of influenza vaccine • Data collection from electronic medical records and immunisation registry database • Vaccination status was included as a time-varying variable using a multivariate Cox proportional hazard model to estimate a HR, this was used because patients continued to be vaccinated during the influenza season • Vaccine efficacy (VE) was calculated as 1 minus HR • Chronic medical conditions included
Participants	Children aged 6 to 23 months
Interventions	Vaccine not specified (see 2003 included strains below) 2003 to 2004 season will include A/New Caledonia/20/99-like (H1N1), A/Moscow/10/99-like (H3N2) and B/Hong Kong/330/2001-like viruses. For the A/Moscow/10/99-like (H3N2) virus, US manufacturers will use the antigenically equivalent A/Panama/2007/99 (H3N2) virus and for the B/Hong Kong/330/2001-like virus, they will use either B/Hong Kong/330/01 or the antigenically equivalent virus B/Hong Kong/1434/02
Outcomes	• ILI for FV children versus UV • P&I for FV versus UV
Funding Source	Government/Industry
Notes	Circulating strain of A (H3N2) Data collected during peak of influenza activity

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
PCS/RCS-Selection Exposed cohort	Low risk	Selected group, secure record
PCS/RCS-Selection Non Exposed cohort	Low risk	Same methods of the exposed cohort
PCS/RCS-Comparability	High risk	Insufficient description

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cb Ritzwoller 2005 (*Continued*)

PCS/RCS-Assessment of Oucome	Unclear risk	Record linkage
Summary assessments	High risk	Some doubt arises from the real comparability of the cohorts

aa Rudenko 1988

Methods	Apparently cluster randomised controlled trial of schoolchildren in the Kalinigrad area of East Prussia (USSR at the time) in 1984-85. The text appears to suggest that children were randomised by class. The participants underwent daily clinical examination for 7 working days after inoculation - recorded temperature, complaints, inspection of skin, mucous from eyes and condition of nasopharynx. Morbidity due to influenza and acute respiratory illness recorded during epidemic period (28/1 to 3/3/85) Antigenic activity determined by inhibition of hemagglutinin by 'standard methods' Daily clinical examination of all children carried out for 7 working days after inoculation Examination recorded temperature and recording of complaints, inspection of skin, recording mucous from eyes and condition of nasopharynx Hematological and biochemical tests and analysis of urine carried out to evaluate safety of vaccine, samples taken before vaccination, 3 days after and 1 month after each dose of vaccine Hematological tests included full blood analysis, thrombocyte count and lymphocyte index Biochemical test included determination of C-reactive protein, protein fraction, neuraminic acid, transaminase alanine-aminotransferase and urea Antigenic activity carried out on subgroup of 240 children Samples taken from 22 children who received vaccine and 18 who received placebo for re-isolation of vaccine Genetic stability of vaccine evaluated from swabs taken from nasopharynx after 1, 2, 3, 7, and 8 days. 3 criteria used - retention of antigenic specificity, temperature sensitive-phenotype, localisation of temperature sensitive-mutations in individual genes of re-isolates Statistical analysis of morbidity carried out using EVM using the criteria of the 'reliability of parameter differences of the binomial distribution' Influenza epidemic from 28/1 to 3/3/85, peak from 11/2 to 17/2/85. Epidemic caused by A(H3N2) (i.e. vaccine did not match circulating strain"
Participants	Children aged 3 to 15 years from nursery schools and schools Participants not inoculated against influenza in previous 3 years
Interventions	Live influenza A(H1N1) vaccine administered intranasally, 2 doses 28 to 30 days apart administered using Smirnov apparatus. An influenza epidemic took place from 28/1 to 3/3/85, peaking from 11/2 to 17/2/85. The epidemic was caused by A(H3N2) (i.e. vaccine did not match circulating strain)
Outcomes	Serological Antigenic activity was determined by HAI, haematological tests included full blood analysis and biochemical tests were also carried out Three serum samples were taken from 240 children to test seroconversion. The basis for the sampling is not described

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aa Rudenko 1988 (*Continued*)

	Effectiveness "Morbidity due to influenza and acute respiratory illness during epidemic period (28/1 to 3/3/85) Morbidity of other illnesses (excluding influenza and ARI) (data not extracted here) Temperature reactions after 7 working days after inoculation Seroconversion, HAI response to virus re-isolates, temperature sensitivity of re-isolates, temperature sensitive-mutations (data not extracted for any of these outcomes)" Safety Reactogenicity was studied in a sample of 596 children after the first dose and in 164 children after the second dose. It is unclear on what basis the children in the samples were selected. The only outcome reported by arm was fever of various degrees but no definition is given
Funding Source	Unclear
Notes	The authors conclude that the vaccine did not affect morbidity because of mismatch between vaccine and circulating viruses. The vaccine also proved to be stable and not very reactogenic. No description of the vaccine content and unclear randomisation and attrition/sampling make the interpretation of the results very difficult

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient descriptions; cluster randomised trial
Allocation concealment (selection bias)	High risk	Not used
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No description
Summary assessments	High risk	No description of the vaccine content and unclear randomisation and attrition/sampling make the interpretation of the results very difficult

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ab Rudenko 1991

Methods	• RCT of live vaccines • Influenza virus B - B/14/5/1 produced by recombination of 2 surface antigens (HA and NA) from epidemic strain B/Ann Arbor/2/86 and 6 "core" antigens from attenuated donor strain B/Leningrad/14/17. Activity of B/14/5/1 7.0 IU of EIE50 in 0.2 ml. (EIE = Experimental Immunogenic Effect in 50% experimental participants) • Commercially available influenza vaccine A (H1N1) A/Taiwan/1/87 also used, with biological activity of 7.0 IU of EIE50/0.2 ml • Children randomised into 4 groups with 1 child serving as a sample unit • All treatments were administered in 2 x 0.5 ml doses by intranasal spray using Smirnov apparatus. 21 interval between first and second doses • Children followed up for 5 days after each dose • Immunogenicity of vaccine determined using reaction of haemagglutinin deceleration and ELISA developed for influenza B virus
Participants	1009 children age 3 to 14 years
Interventions	Influenza virus B - B/14/5/1 (recombinant) Commercial influenza A vaccine - A/Taiwan/1/87 (H1N1)
Outcomes	• Mild fever (31.7 to 37.5°C), moderate fever, malaise, headache, rhinorrhoea, nasal stuffiness, cough, hoarse voice, sore throat, nasal bleeding, conjunctivitis • Seroconversion (data not extracted) • Mean antibody titres (data not extracted) • Increase in ELISA titre (data not extracted)
Funding Source	Unclear
Notes	The text refers to 4 randomised arms with a total denominator of 1009 (this is not a mistranslation as we have checked the original in Arab numerals). Table 2 reports data on 321 children. No mention of the missing children is made. We believe the data is uninterpretable

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No description
Allocation concealment (selection bias)	High risk	Not used
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No description
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No mention of the missing children is made
Summary assessments	High risk	Data are uninterpretable

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aa Rudenko 1993a

Methods	2 years single-blind placebo cluster RCT to assess efficacy of both live cold-adapted and inactivated influenza vaccine
Participants	Children aged 7 to 14 years from 34 schools of Novgorod (USSR). School lists were randomly assigned as whole to one of the vaccine or placebo preparations. The assignment procedure was structured so that different regions of the city would be represented in each immunisation group. The assignment remained the same throughout the study but in the second year new schools were introduced. In the first year a total of 30 schools participated in the study, of which 10 were in the live attenuated group, 9 in the inactivated group and 11 in the placebo group. In the second year of the study the number were respectively 14, 9 and 11. Six of these schools comprised students , who had not participated in the previous year and 1 each of the inactivated vaccine and placebo schools had dropped out. Children aged 7 to 10 in the inactivated group received a more highly purified preparation than those aged 11 to 14. Placebo groups were also divided into 2 subgroups: 1 half was administered placebo intranasally, the other half intramuscularly. In the second year only intranasal placebo was administered
Interventions	• The live attenuated vaccines were reassortant derived from A/Leningrad/134/47/57 (H2N2) and B/USSR/60/69 cold adapted donor strains. For the 1989 to 1990 season the wild type parents of the type A vaccine were A/Sichuan/2/87 (H3N2) and A/Taiwan/1/86 (H1N1) like viruses. For the 1990 to 1991 season wild type A/Shanghai/11/87 (H3N2), A/Taiwan/1/86 (H1N1), B/Victoria/2/87 like were employed. These contained almost 6.25 log10 median EID50 per 0.2 ml. Live vaccine was administered by intranasal spray in 2 doses 3 weeks apart • The inactivated vaccine consisted of undisrupted whole virus inactivated with formalin. Bivalent vaccines were used in the first year and trivalent for the second year of the study. The strains contained in these preparations was antigenically similar to those present in the live attenuated preparations. For the 7 to 10 years old group a chromatographically purified preparation was employed, while the older subgroup were immunised with the whole virus preparation. In the first year the haemagglutinin content was 3 to 8 g of each component, in the second year 7 to 10 g. Inactivated vaccine was administered subcutaneously in the first year and intramuscularly in the second • Placebo consisted of allantoic fluid handled in the same way as vaccines and packaged similarly. To ensure blinding, placebo group was divided in the first year so that children in about half of the schools received intranasal placebo twice, while half received injected placebo once. For the second year it was not possible to obtain approval for an injected placebo and it was all administered intranasally
Outcomes	Serological Paired sera were taken from approximately 100 children during the period preceding the immunisation campaign to test seroconversion Effectiveness “Starting mid-October the nurse in each participating school began to monitor illnesses recorded as acute respiratory disease on medical certificate (required by Russian Schools after an absence). A series of specific respiratory diagnoses was used. Any illness with diagnosis termed as “respiratory illness” or “influenza” was considered a case. Investigation by the polyclinic was conduct if any certificate was provided after an absence from school. When acute respiratory disease increased, virologic surveillance was started to identify influenza viruses

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	To avoid the lack of independence associated with counting multiple illnesses separately, the presence of 1 or more respiratory illnesses in the epidemic period was counted as 1 outcome, whereas the absence of respiratory illnesses during this period was the other outcome. A child receiving vaccine or placebo was included for analysis only if he or she received the full schedule of doses. The 1989 - 90 outbreak of influenza in Novgorod was exclusively A H3N2. the first isolate was made on 15.1.1990 and isolation continued through 22.2.1990. The period used to determine frequency of influenza associated illnesses was 1.1. - 4.3.1990. 12,837 children received full immunisation in the first year. In the school year 1990 - 1991 the influenza outbreak was caused by both types A (A/Taiwan//86 H1N1)and B (B/Yagamata/16/88 or B/Victoria/11/87 like) strains. For the efficacy analysis was considered for the period 14.1 - 24.3.1991 (11 weeks)" Safety "Reactogenicity was assessed 4 days post-inoculation in approximately 100 children during the period preceding the immunisation campaign to test seroconversion Fever During the first year of the study, 1 child out of 162 in the live vaccine group had low-grade fever (< 38.5°C). Any case of fever was observed in the controls and inactivated vaccine group but it was not reported how many participants composed these 2 sub-groups. In the second year low-grade fever was observed in 2 of 323 attenuated vaccine recipients and 2 of 278 placebo recipients and 5 of 271 inactivated vaccine group (age 7 to 10). 8 of the 435 children aged 11 to 14 years (inactivated vaccine, second study year) had also low-grade fever. 3 children of this group had also fever > 38.5°C Induration In the second study year 3 of 271 participants, who received inactivated vaccine (group aged 7 to 10) developed induration as did 17 of 435 in the group aged 11 to 14 These data are not extracted as it is unclear how the children were selected"
Funding Source	Unclear
Notes	The authors conclude that CA live vaccine was more protective than TIV and possibly reduced transmission Randomisation units were schools and results were presented both at cluster (which is right) and individual (which is wrong) levels. How this affects results is impossible to say as no cluster coefficients are reported. Second year study had no intramuscular placebo. This unblinding could have had some effect if different schools were in communication. Data from the pilot reactogenicity cohort (?) study not extracted as provenance and allocation of participants is not clear. Second season inactivated vaccine has no placebo arm and data have not been extracted. No separate reporting of spray and subcutaneous placebo for first year

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No description
Allocation concealment (selection bias)	High risk	Not used

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aa Rudenko 1993a (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not used
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No description
Summary assessments	High risk	Insufficient information

aa Rudenko 1993b

Methods	See Rudenko 1993a
Participants	
Interventions	
Outcomes	
Funding Source	
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No description
Allocation concealment (selection bias)	High risk	Not used
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not used
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No description
Summary assessments	High risk	

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aa Rudenko 1996a

Methods	Cluster randomised controlled trial(s) to determine efficacy and safety of cold adapted flu vaccines prepared with different virus strains. The study was carried out in four steps in USSR (Kalinigrad), Kazakhstan (Alma Ata) and Cuba (Havana). St Petersburg is also mentioned but no results are reported. Neither randomisation nor allocation concealment are mentioned
Participants	Children aged between 3 and 14 years enrolled from schools and kindergartens in St Petersburg, Kalinigrad, Alma Ata and Havana. About 131,930 children were involved in the study
Interventions	Children were randomly divided into groups to receive either live cold adapted influenza vaccine or placebo (2 doses of 0.5 ml, administered 21 to 28 days apart) • Kalinigrad 1986: Intranasal live cold adapted A H1N1 (Virology Department of the Institute of Experimental Medicine, St. Petersburg) 2 0.5 ml doses • Alma Ata 1986 to 87: Intranasal live cold adapted flu A H1N1 A/Brazil/1/79 and H3N2 A/Philippines/1/82; (Virology Department of the Institute of Experimental Medicine, St. Petersburg) 2 0.5 ml doses • Alma Ata 1988 to 89 Intranasal live cold adapted flu A H1N1 A/Brazil/1/79 and H3N2 A/Philippines/1/82; (Virology Department of the Institute of Experimental Medicine, St. Petersburg) 2 0.5 ml doses • Havana 1990 Intranasal live cold adapted flu A H1N1 A/Taiwan/1/86 and B B/Victoria/3/87; (Virology Department of the Institute of Experimental Medicine, St. Petersburg) 2 0.5 ml doses. Havana 1991 • Intranasal live cold adapted flu A H1N1 A/Taiwan/1/86, H3N2 A/Zakarpatie/354/89 and B B/Victoria/3/87; (Virology Department of the Institute of Experimental Medicine, St. Petersburg) 2 0.5 ml doses
Outcomes	Serological "Paired sera tested for seroconversion in subgroups of children and nasal swabs were taken from 22 vaccinated and 18 placebo recipient children to assess spread of vaccination strains (nil result). Haematological and biochemical full blood analysis and urine analysis were carried out on 20 children belonging to each group before vaccination, 3 days after the first dose, 1 month after the first dose, 3 days after the second dose and 1 month after the second dose) IGE determination and lymphocyte functional action assessments were also carried out. " Effectiveness "A nurse in each participating school or kindergarten recorded details of acute respiratory diseases on (from) medical certificates starting in October of each year. A series of specific diagnoses were used. When acute respiratory diseases increased, virological surveillance (blood and nasal swabs) was started to identify influenza viruses. Effectiveness data are reported only for the trials conducted in Alma Ata (1986 to 87 and 1988 to 89) and Havana (1990 and 1991) The first epidemic season in Alma Ata was due to the strain A/Taiwan/1/86 (H1N1) and lasted between November 17th and December 21st. Considering that the epidemic began earlier than expected, it is possible that at this time not all study participants had received the second dose of vaccine or placebo respectively. In the second study year (1988 to 89), the epidemic was caused by the strains A/Taiwan/1/86 and B/Victoria/1/87 and lasted from March 26th 1989 for 9 weeks. In Havana clinical cases of influenza

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	and acute respiratory diseases were registered from December 1st 1990 to December 31st 1991 Efficacy data from Kalinigrad are not reported The only effectiveness outcome reported is ILI" Safety Table 5 reports a long list of common non-ILI ailments which appear to be related to safety for 2 years. These are labelled infectious and somatic diseases up to 6 months after vaccination but are not tied to any specific vaccine or study centre. Similarly Table 3 reports the incidence of febrile reactions by degree of fever and by age for three years without relation to years or vaccine composition. Children were examined for 7 days after vaccination by paediatricians for AEs. Temperature was registered. Data about children, who were immunised for three successive years are reported but have not been extracted as it is unclear which year, which vaccine and most of all how to reconcile massive differences in denominators (for example for year 1, data for a total of 262 children only are reported)
Funding Source	Unclear
Notes	The authors conclude that "the CA vaccines are effective against influenza B and against influenza in general" Febrile reactions and somatic and infectious diseases: To what group or groups belong the children? It is not possible to take back these data with the vaccination plan in table 1 • Influenza and acute respiratory diseases in Havana: Arms in table 8 do not conform to the original randomised arms. Of how many arms consist the Havana trial? Were vaccination carried out in 2 years or were all participants immunised in November 1990? Efficacy data consider a study population aged between 5 and 14. Individuals aged 3 or 4 were apparently not included. Number of children, who received placebo and poli vaccine in table 8 coincide with those showed in the trial Havana 1991 in table 1 but the other are inconsistent • Influenza-like diseases in Alma Ata: Follow-up was probably carried out during the epidemics. Alma Ata 1986 - 87: From table 1 the number of placebo recipients aged 7 to 14 is 18,164. From table 7 results show that 22,963 recipients received vaccine. Could these 2 numbers be erroneously inverted? (and 4799 of the original 22, 963 vaccinated excluded) • Any subject excluded from the safety analysis of 1988 to 89? • What about effectiveness of influenza immunisation in Kalinigrad? Chaotic inconsistent reporting. No attempt at reconciling viral circulation and seroconversion rates with clinical symptoms so it is impossible to assess how many of the ILI episodes are in fact influenza

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient descriptions
Allocation concealment (selection bias)	High risk	Not used

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aa Rudenko 1996a (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Unclear risk	No blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No description
Summary assessments	High risk	Non-sufficient information to assess study design

aa Rudenko 1996b

Methods	• Cluster RCT • Inoculation of children form 16 schools and children's establishments, control groups from 14 schools and 20 pre-school children's establishments • Children observed during vaccination period 06/11/86 to 16/11/86; rise in epidemic 17/11/86 to 21/12/86 and post-epidemic period 22/12/86 to 05/04/87 and number of illnesses recorded • Vaccine administered intranasally using a Smirnov measured sprayer • Efficacy of vaccine assessed by comparing number of cases of influenza and ARI in vaccinated and UV groups and calculating Index of Efficacy using 'generally accepted methods'
Participants	Children aged 3 to 14 years
Interventions	Live recombinant vaccine made from 2 mono vaccine containing A/47/25/1 (H1N1) and A/47/F (H3N2)
Outcomes	• Cases of influenza and ARI • Safety - 18 categories of somatic illnesses up to 6 months after inoculation
Funding Source	Unclear
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient descriptions
Allocation concealment (selection bias)	High risk	Not used
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No blinding

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aa Rudenko 1996b (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No description
Summary assessments	High risk	Non-sufficient information to assess study design

ca Salleras 2006

Methods	Prospective cohort study carried out between 1 November 2004 and 31 March 2005 in 11 paediatric clinics in Barcelona, Spain. The study assessed the effectiveness of virosomal vaccine against ILI and its economic consequences
Participants	966 vaccinated children and 985 non-vaccinated controls attending respectively 5 and 6 clinics. The unit of selection was clinic enrolment. Children were aged 3 to 14 and age breakdown by exposure, sex and by 2 year groupings is reported. Systematic differences are reported (significantly smaller families and younger children in the non-vaccinated cohort). No attrition is mentioned
Interventions	1 dose of virosomal influenza vaccine (Inflexal Berna). Content is not described
Outcomes	Serological Pharyngeal and nasal swabs sent to laboratory for culture. Follow-up was by parents' questionnaire. Follow-up unclear, no mention of how many children were followed up and whether there was attrition in reporting with symptoms Effectiveness • Febrile ARI: fever and respiratory symptoms attended or not by the physician • ILI: children seen by physician with fever greater then or equal to 38.5°C for at least 72 hours, cough and sore throat • Influenza (PCR-confirmed): as per ILI but with positive PCR • Episodes of antibiotic consumption during an acute febrile respiratory illness in the child • Episodes of school absenteeism due to an acute febrile respiratory illness in the child • Episodes of work absenteeism of a family member taking care of a child with an acute febrile respiratory illness in the child Safety N/A
Funding Source	Industry
Notes	The authors conclude that "Adjusted vaccination effectiveness was 58.6% (95% CI 49. 2 to 66.3) in preventing acute febrile respiratory illnesses, 75.1% (95% CI 61.0 to 84.1) in preventing cases of influenza-like illnesses and 88.4% (95% CI 49.2 to 97. 3) in preventing laboratory-confirmed cases of influenza A. The adjusted vaccination effectiveness in reducing antibiotic use (18.6%, 95% CI -4.2 to 3.64), absence from school (57.8%, 95% CI 47.9 to 65.9) and work-loss of parents (33.3%, 95% CI 8.9 to 51.2) in children affected by an acute febrile respiratory illness was somewhat lower. Vaccination of children aged 3 to 14 years in paediatric practices with 1 dose of virosomal

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ca Salleras 2006 (*Continued*)

	subunit inactivated influenza vaccine has the potential to considerably reduce the health and social burdens caused by influenza-related illnesses". Systematic differences ("adjusted with logistic regression") between hemicohorts lack of description of vaccine content, matching and influenza circulation make the conclusions unreliable. Why use PCR? Was the quantity of viral genome so tiny to need amplification?

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
PCS/RCS-Selection Exposed cohort	Unclear risk	Selected group
PCS/RCS-Selection Non Exposed cohort	Unclear risk	Same methods but different population
PCS/RCS-Comparability	High risk	Clearly different populations, no adjustments
PCS/RCS-Assessment of Oucome	Unclear risk	ILI self-reported
Summary assessments	High risk	Some doubt arises from real comparability of the cohort

ab Slepushkin 1974

Methods	Placebo and do-nothing-controlled emergency randomised trial of live attenuated oral influenza vaccine carried out during the 1970 to 1971 season in Smolensk, USSR. During January 1971, at the beginning of an epidemic of influenza in the town, oral vaccination was carried out as an emergency on organised groups of children of nursery school age (1 to 3 years) and it appears that this study carried out only in 2 arms is the one for which we have data reported in the tables. The vaccine was given 2 to 3 times with an interval of 10 to 15 days. There appears to be another study included in the report to assess the effectiveness of the vaccine(s) in inducing interferon (Data not extracted)
Participants	The children in each establishment (childrens' nurseries, nursery groups in larger schools) were selected on a medical basis and their temperature was measured. Although the text states that "Three equal groups of healthy children were formed at random" the tables report 571 and 552 children in the vaccine and "UV" groups respectively. It could be that the 3-arm trial is different from the trial undertaken in January 1971 but the text is very confusing. There may even be a fourth study with again 3 arms
Interventions	For the vaccination, 2 types of the oral influenza vaccine were used, which were analysed at the Moscow Institute of Virological Preparations. The vaccine was composed of the strains of the influenza virus A2/Istra 10/96 and B/Liks 59, the infectious titre 10 exp.5.5 (The "two types" are not further discussed or reported. The single dose of the emergency prophylaxis vaccine for children was 1 ml for children aged 1 to 3 years, 2 ml for children aged 3 to 7 years and 3 ml for children aged 8 to 16 years

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Outcomes	Serological "In order to determine antibodies, blood serum was taken from those who had been inoculated, before vaccination and between 21 to 30 days after its completion. The blood serum was tested in a reaction of the inhibition of the hemagglutination with 1% red corpuscle from chickens and four units of hemagglutinins of the virus when the antigen was put into contact with the antibodies for two hours" Effectiveness Follow-up was 45 days. The children in the first group received the live influenza vaccine and the second group received the medium no. 199, applied in the capacity of placebo. The third group were those who were not inoculated. For each child records were maintained, containing the date of inoculation, the type of vaccine and also information about reactions to the vaccine. This included the results of the contraction of acute respiratory illnesses, starting from 10 days after the completion of the inoculations Study 1 • Raised temperature up to 37.5°C, number of days after vaccination not defined • Raised temperature > 37.5°C, number of days after vaccination not defined • Contraction of influenza and other acute respiratory illness >/= 10 days after inoculation • 4-fold rise in hemagglutination antibody titre (not for data extraction) Study 2 • Emergency prevention of illness in first 15 days after vaccination (data not extracted, confounders, some children must have been sick over period of administration of 3 doses of vaccine, also no placebo arm carried out) Safety "The reactogenicity of the vaccine was determined by measuring daily the temperature in certain groups of those who had been inoculated"
Funding Source	Unclear
Notes	The authors conclude: 1. "The establishment of the weak reactogenicity of the Moscow Scientific Research Institute of Virological Preparations' (MNIIVP) live oral influenza substance for children aged 1 to 3 years and children of school age 2. The study of the efficacy of MNIIVP's live oral influenza vaccine as an inductor of endogenic interferons 3. In 1970, during the rise in the cases of influenza and acute respiratory illnesses, administering the vaccine twice and three times reduced the rate of illness in pre-school childrens' establishments by twice, compared with those not vaccinated and by 1.5 times compared with the group of children who received placebo 4. During the winter rise in the number of cases of respiratory virus infections in 1972, MNIIVP's live oral influenza vaccine reduced the number of cases in the pre-school group by 10.9 times after the first administration and by 4.4 times after the second. No noticeable effect was recorded after the third administration of the vaccine (index of efficacy 1.3) 5. The index of efficacy of the live oral influenza vaccine used for the emergency prophylaxis of school children was precisely 4.0 and 2.7, after the first and second administrations respectively 6. Using complex prophylactic methods (the routine immunisation in autumn,

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ab Slepushkin 1974 (*Continued*)

	combined with the emergency prophylaxis) increased the efficacy of the live oral influenza vaccine by 2 times 7. MNIIVP's live oral influenza vaccine substance is recommended for extreme prophylaxis of influenza and viral acute respiratory illnesses in pre-school (aged from 1 to 7 years) and school aged children" The text is so confusing that only the data from the tables have been extracted. However, we are not sure of its relationship with the text

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	High risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not described
Summary assessments	High risk	Insufficient information to assess study design

ab Slepushkin 1988

Methods	Randomised, single-blinded placebo-controlled study conducted in a boarding school in Moscow in September to December 1984
Participants	107 healthy children 8 to 11 years old, without a history of current illness were examined and judged eligible for this study
Interventions	Attenuated influenza vaccine prepared by recombination of the cold-adapted strain A/Leningrad/134/47/57 (H2N2) with A/Leningrad/322/79 (H1N1). Before use, lyophilised vaccine was diluted 1:2 with distilled water and administered intranasally by means of a Smirnoff aerosol generator. Distilled water only was administered as placebo. 2 doses of 0.5 ml were administered 28 days apart. Vaccine titre was 102 EID50 for the first dose and 107 for the second. Participants were randomly divided to receive vaccine or placebo. 58 children received the first dose of vaccine and 49 placebo. Of the 58 vaccinated children, 43 received second dose of vaccine and 39 of 49 received second dose of placebo
Outcomes	Serological Hemagglutination inhibition test against A/Brasil/11/78 and Enzyme immunoassay Effectiveness

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ab Slepushkin 1988 (*Continued*)

	N/A Safety "All children were observed for 5 days after each vaccination Axillary temperature was measured once each day and children were interviewed about the presence of eventual symptoms and visited at home in case of absence from the school"
Funding Source	Government
Notes	The authors conclude that despite the first dose being weekly immunogenic, the second dose response was much better and the vaccine proved safe. Poorly conducted study: de facto unblinded, with unexplained attrition. Physical aspect of placebo and vaccine in coded vials was different making blinding inadequate. There is a strange subanalysis of respiratory symptoms classified as harms by arm after the first vaccination dose. The authors carried out nasal swabs in 10 children and found that 1 had tonsillitis and 5 had adenovirus rhinitis. Although the breakdown by arm of these is not reported as this is a RCT, what surely matters is the difference in event between arms, even for harms. This leads me to suspect that the authors did not trust their own random allocation

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	High risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unexplained losses to follow-up
Summary assessments	High risk	Poorly conducted study: de facto unblinded, with unexplained attrition

ab Slepushkin 1991

Methods	Randomised placebo-controlled trial carried out in the 1987-1988 season in Leningrad, former USSR on school children aged 8 to 15 years to test live CA vaccine, with inactivated vaccine with intranasal and intramuscular placebo (data by placebo not presented split). There was an influenza A (H3N2) and B mixed epidemic reported in Slepushkin 93 but the vaccines did not contain any B antigen. Influenza A peaked in mid Jan to mid Feb, whereas circulation of influenza B was constant

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ab Slepushkin 1991 (*Continued*)

Participants	241 healthy boarding school children aged 8 to 15 years (97, 56, 88 (for CA, bivalent vaccine and placebo at first dose and 95 and 78 for CA and placebo). The attrition between first and second dose of both active arm and placebo is not explained
Interventions	Intranasal live CA A/47/F derived from A/Philippines/2/82-like (H3N2) and A/Leningrad/134/47/57 (H2N2) or intramuscular normal saline placebo or bivalent vaccine (containing A/Philippines/2/82-like (H3N2) and A/Chile/1/83/ (H1N1) or intranasal allantoic fluid placebo. IM applications took place only once, whereas internasal twice approximately 4 weeks apart
Outcomes	1. Temperature 2. Local reactions Serological Paired sera and "micro neutralisation test". Convalescent sera only on those children who reported with ILI symptoms to the school nurse Effectiveness N/A in Slepushkin 1991, effectiveness was reported in Slepushkin 1993 for school 1: those children reporting with ILI (systemic illness or rhinitis or pharyngitis) symptoms had convalescent sera taken. Also reported are data from another school in the trial with asymptomatic cases (i.e. no symptoms but antibody rises). This is strange as the asymptomatics are all occurring in 1 school and the explanation is in the text: data on clinical illness were not collected. DATA NOT EXTRACTED Safety Temp (37.1°C to 37.5°C), local reactions, headache, sore throat, cough, head cold
Funding Source	Government
Notes	The authors conclude that "The inactivated vaccine was found to be superior to the live one in its capacity to stimulate humoral immunity studied by HI, EIA and microneutralisation tests. In 69.7% of the children given the inactivated vaccine, seroconversion to the vaccine strain was detected by 2 or three methods of antibody titration used." Randomisation and attrition are not explained. Briefly reported study but clear text. The authors checked harm data against seroconversion, to ensure that for example temperature was not associated with seroconversion i.e. with infection. Unfortunately no effectiveness data are reported. Follow-up not described. Problem with data collection and surveillance in school 2. In the 1993 paper the authors report efficacy as 13% (P = 0.82) for 2 doses of CA and 73% (P = 0.08) for 1 dose of bivalent vaccine. This relates to school 1. They also report an efficacy estimate for school 2 but this is likely to be highly unreliable

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Insufficient descriptions

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ab Slepushkin 1991 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not described
Summary assessments	Unclear risk	Randomisation and attrition are not explained

cb Slepushkin 1994

Methods	Cohort study to compare reactogenicity and immunogenicity in children vaccinated with live vaccine, inactivated vaccine or placebo carried out over 3 years in Novogorod, former USSR. No mention of randomisation is made and the study was classified as a cohort. Allocation was on a school basis. A subgroup was inoculated each year of study prior to mass inoculations to determine reactogenicity and immunogenicity. Reactogenicity and immunogenicity results were analysed using 'generally accepted methods' (Slepushkin et al 1991, Ibid, 5: 372-4)
Participants	Children aged 7 to 14 years
Interventions	• 1989 - Soviet Commercial bivalent-vaccine A/Sichuan/2/87-like (H3N2) and A/Taiwan/1/86-like (H1N1) - inactivated • 1989 - Soviet Commercial bivalent -vaccine A/Sichuan/2/87-like (H3N2) and A/Taiwan/1/86-like (H1N1) - live • 1990 - A/Shanghai/11/87 (H3N2), A/Taiwan/1/86 (H1N1), B/Victoria/2/87 - inactivated • 1990 - A/Shanghai/11/87 (H3N2), A/Taiwan/1/86 (H1N1), B/Victoria/2/87 - live • 1991 - A/Shanghai/11/87 (H3N2), A/Taiwan/1/86 (H1N1), B/Victoria/2/87- inactivated • 1991 - A/Shanghai/11/87 (H3N2), A/Taiwan/1/86 (H1N1), B/Yamogota/16/88-like - live THERE IS NO PLACEBO ARM REPORTED IN THE THIRD YEAR, WHICH IS STRANGE AS THERE IS A PLACEBO ARM REPORTED FOR IMMUNOGENICITY IN TABLE 2. FOR THE SECOND YEAR THERE IS ALSO A MYSTERIOUS SECOND INACTIVATED VACCINE WHICH APPEARS IN THE RESULTS TABLES - DATA NOT EXTRACTED To obtain live recombinant vaccine, cold-adapted strains A/Leningrad/134/47/57 (H2N2) and B/USSR/60/69 were used as attenuation donors
Outcomes	Serological Seroconversion (not extracted) Effectiveness N/A Safety Temperature reactions and local hyperemia and infiltration after vaccination

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cb Slepushkin 1994 (*Continued*)

Funding Source	Government
Notes	The authors do not draw clear conclusions and it is difficult to understand what the purpose of the study was. Badly reported, no clear overall denominator and safety data is reported for limited groups of participants with no clear sampling rule

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
PCS/RCS-Selection Exposed cohort	Unclear risk	No description
PCS/RCS-Selection Non Exposed cohort	Unclear risk	No description
PCS/RCS-Comparability	Unclear risk	No description
PCS/RCS-Assessment of Oucome	Unclear risk	No description
Summary assessments	High risk	Insufficient information

ca Slobodniuk 2002a

Methods	"Cohort study of inactivated trivalent influenza vaccines compared with no treatment over 3 years. An additional aim of the study was to assess the impact on the immune system of vaccinating children for 3 years in a row. Children were immunised during three epidemics in 1998, 1999 and 2000 and controls were students from parallel classes, who received no intervention. The efficacy of the vaccines was determined from total morbidity rate for influenza and ARIs during outbreak periods 25/01/99 to 14/03/99; 10/01/00 to 21/02/00 and 21/01/01 to 23/02/01 in a boarding school in Yekaterinburg, Russia"
Participants	564 pupils of the boarding school aged 8 to 14 years
Interventions	• In 1998 to 1999 and 1999 to 2000 seasons 'Fluarix' inactivated commercial vaccine (Smith Kline Beecham) containing A/Singapore/6/86 (H1N1), A/Beijing/32/9 (H3N2) and B/Panama/45/90 was used • In 2000 to 2001' Grippol' polymer sub-unit vaccine containing influenza virus strains A1, A3 and B was used
Outcomes	Serological Immune response was evaluated before and 30 days after receiving the vaccine. Tests were carried out by serological status (i.e. in seropositive and seronegative children) in 70 children in year 1, 109 in year 2 and 73 paired sera in year 3 Effectiveness Number of children with influenza or ARI during outbreak period each year Safety N/A

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ca Slobodniuk 2002a (*Continued*)

Funding Source	Unclear
Notes	The authors conclude that the vaccines offered increased protection with each new season, in effect having an additive effect. The first season the efficacy of Fluarix was low in the epidemic period (1.3?), the second inoculation achieved 2-fold protection compared to the control group. The final year Grippol reduced morbidity by 2.8 times. According to the authors a fourth injection could be unnecessary. The study is very difficult to interpret, there is no information on participants, community, matching, viral circulation disparity between paired sera and enrollees etc

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
PCS/RCS-Selection Exposed cohort	Unclear risk	Not described
PCS/RCS-Selection Non Exposed cohort	Unclear risk	Not described
PCS/RCS-Comparability	Unclear risk	Not described
PCS/RCS-Assessment of Oucome	Unclear risk	Not described
Summary assessments	High risk	Insufficient information to assess study design

ca Slobodniuk 2002b

Methods	See Slobodniuk 2002a
Participants	
Interventions	
Outcomes	
Funding Source	
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
PCS/RCS-Selection Exposed cohort	Unclear risk	Not described
PCS/RCS-Selection Non Exposed cohort	Unclear risk	Not described

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ca Slobodniuk 2002b (*Continued*)

PCS/RCS-Comparability	Unclear risk	Not described
PCS/RCS-Assessment of Oucome	Unclear risk	Not described
Summary assessments	High risk	Insufficient information to assess study design

ca Slobodniuk 2002c

Methods	See Slobodniuk 2002a
Participants	
Interventions	
Outcomes	
Funding Source	
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
PCS/RCS-Selection Exposed cohort	Unclear risk	Not described
PCS/RCS-Selection Non Exposed cohort	Unclear risk	Not described
PCS/RCS-Comparability	Unclear risk	Not described
PCS/RCS-Assessment of Oucome	Unclear risk	Not described
Summary assessments	High risk	Insufficient information to assess study design

ab Steinhoff 1990

Methods	Randomised, double-blind, placebo-controlled trials of intranasal avian-human and cold-adapted vaccines. Conducted separately in a step-wise, dose-escalating fashion
Participants	63 seronegative (HAI no more than 1:8 to H3N2) children aged 6 to 48 months
Interventions	• Cold-adapted (ca) (H3N2) intranasal reassortant virus vaccine A/Ann Arbor/6/60 x A/Bethesda/1/85 (H3N2) • Avian-human (ah) (H3N2) intranasal reassortant virus vaccine A/Mallard/New York/6750/78 x A/Bethesda/1/85 (H3N2) Both vaccines diluted in L-15 medium (Whitaker Bioproducts, Walkersville, MD) Placebo was L-15 medium

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ab Steinhoff 1990 (*Continued*)

Outcomes	Serological Paired sera, duration of viral nasal shedding, production of mucosal antibodies Effectiveness N/A Safety • "Fever: temperature at least 38.1°C, within 7 days of vaccination • Influenza-like illness: fever, upper respiratory tract illness or lower respiratory tract illness on 2 or more consecutive days, within 7 days of vaccination • Upper respiratory tract illness: rhinorrhoea, pharyngitis or both, within 7 days of vaccination • Otitis media: loss of normal tympanic membrane landmarks and decreased mobility determined by 2 independent examiners, within 7 days of vaccination • Illness attributable to influenza A virus - laboratory-confirmation of influenza A infection, within 7 days of vaccination • Influenza infection from vaccine (data not extracted) • Serum antibody response (data not extracted) • Nasal wash antibody response (data not extracted) • Isolation of vaccine virus (data not extracted)"
Funding Source	Government
Notes	The authors conclude that the vaccines are safe and induce immunity, protecting participants from challenge with homologous virus • A viral challenge study was also carried out (data not extracted) • Sensitivity analysis by vaccine concentration (data not extracted)

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Double-blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up
Summary assessments	Unclear risk	Insufficient information to assess study design

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ab Steinhoff 1991

Methods	"RCT to compare characteristics of 2 live reassortant vaccines: cold-adapted (ca) and avian-human (ah) Vaccines were manufactured by isolating wild-type A/Kawasaki/9/86 (H1N1) in tissue culture and four times passage in tissue culture and once in eggs. These were crossed with donor strains to produce reassortant vaccines. Each vaccine was diluted in L-15 medium (Whitaker Bioproducts) to achieve desired number of infectious units Vaccines were evaluated in 1987 and 1988 during periods when no influenza viruses were circulating. Vaccines initially tested in young adults (data not extracted) before continuing with children's study"
Participants	122 children aged 6 to 24 months seronegative to A/Kawasaki/86 (H1N1) were randomised to receive a first dose of either ah (40 children), ca (39) or placebo (43)
Interventions	• Avian-human (ah) reassortant vaccine A/Kawasaki/9/86 (H1N1) x A/Mallard/New York/6750/78 (H2N2) • Cold-adapted (ca) reassortant vaccine A/Kawasaki/9/86 (H1N1) x A/Ann Arbor//6/60 (H2N2) • Vaccines were administered in dose-escalating fashion, after each dose shown to be safe, 10-fold higher dose administered until dose of 106 TCID50 was reached • Each child received 1 0.5 ml dose (0.25 ml per nostril) • Children were observed for 1 to 2 hours daily for 3 days before inoculation and 7 to 9 days after each dose shown to be safe, 10-fold higher dose administered until dose of 106 TCID50 was reached
Outcomes	Serological "Isolation and identification (by HAI assay) of virus from vaccine (data not extracted) Antibodies in sera and nasal washes (or nasopharyngeal swabs) by HAI assay and ELISA (data not extracted)" Effectiveness N/A Safety • Fever (rectal temperature at least 38.1°C) • Fever (rectal temperature at least 39.4°C) • Upper respiratory tract illness (rhinorrhoea, pharyngitis or both) • Lower respiratory tract illness (persistent, wheezing or cough) for at least 2 consecutive days • Otitis media • Children were observed for 1 to 2 hours daily for 3 days before inoculation and 7 to 9 days after"
Funding Source	Government
Notes	The authors conclude that the ca A/Ann Arbor/6/60 donor virus reliably confers attenuation characteristics to a variety of H1N1 and H3N2 influenza A viruses. No description of randomisation, allocation, attrition or placebo. Data on adults were not extracted. Data by TCID not extracted separately. Data on ILI with or without infection were extracted as these are responses to viral challenge

Risk of bias	***Risk of bias***

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ab Steinhoff 1991 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up
Summary assessments	Unclear risk	Insufficient information to assess study design

ab Swierkosz 1994

Methods	Randomised, double-blinded, placebo-controlled trial to assess safety of adding a third dose of a live attenuated, cold-recombinant, trivalent influenza vaccine
Participants	22 healthy infants and children aged 2 to 22 months were recruited. 17 were seronegative to all three hemagglutinin types, while 2 were seronegative to H3 and B and 2 were seronegative to H1 and B
Interventions	Subjects were randomised to receive 3 doses of 0.5 ml vaccine or placebo intranasally in a double-blinded way. 17 healthy infants and children received vaccine and 5 received placebo. Vaccine was administered at day 0, day 60 and day 120. Vaccine contained three strains: A/Kawasaki/9/86 (H1N1), A/Los Angeles/2/87 (H3N2) and B/Yamagata/16/88. The vaccine lots contained 108.0, 108.0 and 107.6 TCDI50/ml H1N1, H3N2 and B. 106 TCDI50 of each strains was present in 0.5 ml of trivalent vaccine
Outcomes	Serological "HAI titres against H1, H3, B and all types (H1, H3 and B) after first dose at day 0, second dose at day 60 and third dose at day 120 ELISA response to H1, H3, B and to all types (H1, H3 and B) after dose first dose at day 0, after second dose at day 60 and third dose at day 120" Effectiveness N/A Safety Adverse reactions were defined as fever (rectal temperature > 38.3°C, or > 37.2°C axillary) ; cough (2 or more episodes during examination on 2 consecutive days); otitis media (red immovable ear drum diagnosed by pneumotoscopy); and lower respiratory tract infection as indicated by wheezing (sustained musical sound during expiration) or pneumonia (a new alveolar consolidation seen radiographically). Clinical observations were recorded daily for 11 days

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ab Swierkosz 1994 (*Continued*)

Funding Source	Government
Notes	The authors conclude that trivalent, cold adapted intranasal influenza vaccine is safe and immunogenic, when administered in a three dose regime. A tiny schedule-ranging trial. Only 4 participants were aged less than 6 months

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not described
Summary assessments	Unclear risk	Insufficient information to assess study design

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aa Tam 2007a

Methods	Multicentre (8 centres in Southeast Asia: China, Hong Kong, India, Malaysia, the Philippines, Singapore, Taiwan and Thailand) RCT carried out over three seasons (enrolment and follow-up was carried out between 30 September 2000 and 31 May 2003) to assess efficacy, immunogenicity and safety of live recombinant vaccine in small children. The randomisation schedule for each year was generated by Wyeth • In year 1, vaccine and placebo were labelled with 1 of 5 treatment codes, 3 of which corresponded to CAIV-T treatment and 2 to placebo, to ensure blinding with a 3:2 ratio. At enrolment, each subject was assigned the next sequential subject number and received study product of the treatment code assigned to that subject number according to a preprinted randomisation allocation list • In year 2, randomisation at each site was accomplished using an interactive voice response system. Trial personnel telephoned the interactive voice response system to obtain a 6-digit vaccine identification number corresponding to nasal sprays mailed to that site and numbered according to a predetermined randomisation list. The per-protocol (PP) population in year 1 included all randomised participants who received all doses of assigned treatment and who remained in the study for at least 15 days after receiving the second dose of CAIV-T or placebo • The PP population in year 2 included all re-randomised participants who received their assigned treatment and remained in the study for at least 15 days after vaccination in year 2 • The intent-to-treat population in year 1 included all participants who were enrolled in the study and received at least 1 dose of study treatment. The year 2 intent-to-treat population included all participants re-randomised in year 2
Participants	Starting from 30 September 2000, 3174 children aged 12 to 36 months were enrolled and allocated either to CAIV (1900) or to placebo (1274). Each year the participants were re-randomised to either placebo or vaccine at a ratio of 2:3 • The year 1 PP efficacy population was 2764 participants (1653 CAIV-T and 1111 placebo) • In year 2, 2947 participants were re-randomised either to a single dose of CAIV-T or placebo from 9 November 2001 • The year 2 PP efficacy population was 2527 participants. 69 participants from year 1 were not randomised in year 2 but were followed up for safety and influenza surveillance throughout year 2. Detailed participant flow with reasons for exclusion from PP analysis is reported in Web-only supplementary materials. Participating children had evenly mixed genders (46% vs 53%) and were mainly of Chinese (36.1%) , Filipino (26.5%) or Thai (29.4%) ethnicity Mean age at first vaccination is reported as 23.5 (SD 7.4) months which is strange, as if the enrollees are always the same, most of them should have been out of age by the second season • In year 1, participants were randomised 3:2 (CAIV-T: placebo) to receive 2 doses of CAIV-T or 2 doses of placebo at least 28 days apart using a randomisation schedule generated by Wyeth • In year 2, participants 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. Although there is a very detailed figure (2) representing viral isolates in the 2 seasons in countries in which the study took place and comparison with study isolates, it is unclear how country-surveillance was carried out and how these relate to study isolated strain. The matching of the vaccines for both seasons is described as not matching for

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	strain B and only partial for A viruses Figure 1 is not fully explained in the text. It shows four groups at year 2 with differing sequences of allocation to CAIV-T and placebo. The initial trial description is that of a crossover but that is not fully explained in the text as well as the 3rd year of the study which disappears in the folds of the text
Interventions	• Intranasal CAIV-T (MedImmune) containing A/New Caledonia/20/99 (H1N1), A/Sydney/05/97 (H3N2) and B/Yamanashi/166/98 (year 1) and A/New Caledonia/20/99 (H1N1), A/Panama/2007/99 (H3N2) and B/Yamanashi/166/98 influenza strains (year 2). The vaccines used were refrigerated formulations of CAIV-T vaccine made Wyeth. The vaccine contained no preservatives • Placebo was sterile physiological saline (Wyeth) Both CAIV-T and placebo were supplied in identically packaged sprayers; study participants, their parents or guardians and the clinical personnel were blinded. Although vaccine content was planned to be antigenically representative of the WHO recommendations for the Northern Hemisphere for each year. "However, in year 1, because of industry-wide technical problems in the production of the A/H3N2/Moscow/10/99-like virus, A/H3N2/Panama/2007/99 vaccine virus, the recommended strain was replaced with A/H3N2/Sydney/05/97.25 This decision was based on the antigenic similarity of the hemagglutinin (HA) antigens, a WHO report indicating that A/H3N2/Sydney/05/97-like viruses were circulating before the 2000 to 2001 season, 26 and previous clinical trials with the frozen formulation of LAIV that had demonstrated efficacy against mismatched influenza A/H3N2 virus. In year 2, because of delays in manufacture, the recommended B vaccine component, B/Victoria/504/2000 (B/Sichuan/379/99-like), was replaced with B/Yamanashi/166/98. Therefore, the B component of the second-year vaccine formulation was not antigenically representative of the B/Victoria/504/2000 (B/Sichuan/379/99-like) virus recommended by the WHO for the upcoming influenza season" In summary the vaccines in both years were not well matched
Outcomes	Serological Paired sera were taken from 111 participants at 5 sites. However "the same participants did not necessarily participate in the cohort in both years". Blood samples were obtained before and after the second vaccination in year 1 and before and after vaccination in year 2. In summary it is unclear what the relationship of these participants is with the rest of the study population. Nasal swabs were taken from symptomatic ILI cases Effectiveness The primary efficacy end point was the first episode of culture-confirmed influenza illness caused by a subtype antigenically similar to that in the vaccine after receipt of the second dose of study vaccine or placebo during year 1 in the PP population. Secondary efficacy end points included the first episode of culture-confirmed influenza illness caused by any influenza virus subtype after receipt of the second dose of study vaccine or placebo during year 1 and the first episode of culture-confirmed influenza caused by subtypes. It is unclear whether follow-up included all participants with ILI symptoms. The text reports follow-up was carried out by phone and clinic visits Safety Parent or legal guardians recorded daily symptom information for 11 consecutive days including the day of administration. AEs were defined as any clinically significant event, including but not limited to (1) events requiring prescription or nonprescription medi-

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	cation within 11 days of vaccination, (2) any event requiring an unscheduled healthcare provider visit and/or consultation within 11 days of vaccination, (3) events resulting in study termination and (4) any other clinically significant event occurring at any time during the course of the study. SAEs, including hospitalisations, were monitored from enrolment until the end of the study. Fever, runny nose, decreased activity or appetite and use of increased fever medications. Other outcomes reported were bronchospasm (7 CAIV-T, 3 placebo), bronchitis (3 CAIV-T, 2 placebo) and rhinitis (3 CAIV-T, 0 placebo) in year 1. In year 2 a child was hospitalised with pneumonia 6 days after receiving CAIV-T. There was 1 dropout (20-month-old female developed fever that persisted for 3 days) after receiving the first dose of CAIV-T in year 1. There were 2 deaths unrelated to vaccine. Perusal of reported safety denominators in Table 6 show the usual discrepancies in trials of these CAIV-T vaccines- denominators that are reported as ranges with the usual (see Vesikari) caption "†n represents the number of participants with known values". According to Table 6, 1345 received CAIV-T in season 2 but according to Figure 1 the total should be 1757. There is no mention of the fate of the other children
Funding Source	Industry
Notes	The authors conclude that "In year 1, efficacy of CAIV-T compared with placebo was 72.9% [95% confidence interval (CI): 62.8 to 80.5%] against antigenically similar influenza subtypes and 70.1% (95% CI: 60.9 to 77.3%) against any strain. In year 2, revaccination with CAIV-T demonstrated significant efficacy against antigenically similar (84.3%; 95% CI: 70.1 to 92.4%) and any (64.2%; 95% CI: 54.2 to 77.3%) influenza strains. In year 1, fever, runny nose/nasal congestion, decreased activity and appetite and use of fever medication were more frequent with CAIV-T after dose 1. Runny nose/nasal congestion after dose 2 (year 1) and dose 3 (year 2) and use of fever medication after dose 3 (year 2) were the only other events reported significantly more frequently in CAIV-T recipients. CAIV-T was well tolerated and effective in preventing culture-confirmed influenza illness over multiple and complex influenza seasons in young children in Asia. Randomisation and allocation concealment are described very well but inconsistencies in the text (a vanished season), unclear denominators and a real possibility of biased follow-up and reporting bias of safety outcomes make this study at high risk of bias. Safety remains a concern in these studies with bronchospasm a possible AE

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random number
Allocation concealment (selection bias)	Low risk	"At enrolment, each subject was assigned the next sequential subject number and received study product of the treatment code assigned to that subject number according to a preprinted randomisation allocation list"

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aa Tam 2007a (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Possibility of biased follow-up and reporting bias
Summary assessments	Low risk	Plausible bias unlikely to seriously alter the results

ca Vasil'eva 1982

Methods	Comparative cohort study of a monovalent injected vaccine in children aged 7 to 15 years in Leningrad, former USSR. The setting, season and viral circulation are not described
Participants	335 children of unknown provenance
Interventions	Monovalent inactivated vaccine containing A/Texas/1/77 (H3N2) (Leningrad Louis Pasteur laboratories) subcutaneous or by needless injector or placebo. Placebo is not described
Outcomes	Serological Paired sera taken in a non-described fashion. There were antibody rises to other influenza A viruses and PIV 1 in the placebo arm Effectiveness ILI described in the translation as "influenza and URTI". Breakdown by age groups and type of injection is not reported Safety Temperature, induration, headache, malaise, sore throat. Daily physical examinations for 5 days
Funding Source	Unclear
Notes	The authors conclude that the vaccine (incidence in the arms was 1.8 and 9.9 respectively) was effective, immunogenic and safe. Very brief report. There is no description of randomisation, allocation or attrition. The authors briefly described evidence of A/Khabarovsk/77, A/Texas/77 and PIV 1 circulation in the placebo arm which could account for some of the febrile episodes

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
PCS/RCS-Selection Exposed cohort	Unclear risk	Not described
PCS/RCS-Selection Non Exposed cohort	Unclear risk	Not described

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ca Vasil'eva 1982 (*Continued*)

PCS/RCS-Comparability	Unclear risk	Not described
PCS/RCS-Assessment of Oucome	Unclear risk	Not described
Summary assessments	High risk	Insufficient information to assess study design

ab Vasil'eva 1988a

Methods	RCT assessing reactogenicity and immunogenicity of bivalent vaccine "RCT of inactivated influenza vaccine; large-scale study of the effect of multiple immunisations on immunity. Children were randomised in groups for safety evaluation. Children were randomised (in sub-group) as individuals for immunogenicity evaluation. Vaccination was carried out once, twice, 3 times, 3 times with interval of 2 years, 4 times but sub-groups only were evaluated for 5 days after inoculation; measuring temperature, local reactions and subjective complaints Data on long-term consequences, somatic and infectious disease (excluding influenza and ARI) and allergies were collected from all participants over a 6 month period after inoculation. Sub-groups were monitored for any admissions to hospital during 30 days following immunisation"
Participants	12,643 children aged 11 to 14 years from Rostov-on-Don recruited during the period Oct 1984 to May 1986
Interventions	BBivalent inactivated, chromatographic, influenza vaccine A/Philippines/82 (H3N2) and A/Kiev/59/79 (H1N1)
Outcomes	Serological Immunological tests (with determination of concentration of IGA, IGE and IGM) were carried out on a subgroup. 'Allergising effect' of vaccine determined by measuring IgE by radio-immunological method and antibodies towards chicken embryos in hemagglutination neutralisation reaction Effectiveness N/A Safety • "Increase in temperature within 5 days of inoculation • Intoxication and catarrh in nasopharynx within 5 days • Hyperaemia within 5 days • Infiltration within 5 days • Pain at administration site within 5 days • Requests for urgent medical attention within 30 days • Hospitalisation within 30 days • Morbidity due to nosological disease (excluding influenza and ARI) within 30 days although not entirely clear from text • Increase in antibody titre - chicken embryo protein (data not extracted) • Increase in antibody titre - parainfluenza (data not extracted)"
Funding Source	Unclear

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ab Vasil'eva 1988a (*Continued*)

Notes	The authors conclude that multiple immunisations with bivalent vaccine do not have an immunity suppressing effect. Unclear rationale for subgroup sampling and sketchy description of methods. Much may have been lost in translation

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient descriptions
Allocation concealment (selection bias)	High risk	Not used
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No description
Summary assessments	High risk	Unclear rationale for subgroup sampling and sketchy description of methods

ab Vasil'eva 1988b

Methods	Randomised, placebo-controlled trial carried out during 1983 to 1984 in the area of Rostov-on-Don in the former USSR. The study was conducted to assess efficacy, effectiveness, safety and immunogenicity of 2 types of bivalent vaccine versus placebo. These were administered by injection and needleless injector, although the data is presented by what the translator calls "chromatographic", "centrifugal" and "adsorptive" types of vaccines, elsewhere they are reported as whole virion vs split. Randomisation is described only to say that older children ("adolescents") were drawn individually into the randomisation sequence whereas children aged 11 to 14 were selected on the basis of their class. It is unclear whether this means cluster randomisation although denominators are roughly on a 3:1 basis. There was a B virus epidemic in January 1984 and then a H1N1 epidemic reported in Rostov-on-Don
Participants	13,355 children aged 11 to 14 and "teenagers" observed of which 9962 took part in the vaccine evaluation (explanation not given). 6596 were randomised to vaccines and 3393 to placebo. However there are several inconsistencies in the text (see outcomes). The participants were recruited from schools, professional technical establishments and technical colleges in Rostov-on-Don, Taganrog and Novocherkassk
Interventions	Bivalent vaccine whole virion or split ("formed from the influenza virus strains A/Leningrad/385/80 (H3N2) and A/Kiev/79 (HINI): chromatographic, centrifugal and adsorbitive(?) chemical influenza vaccines") or placebo ("sterile apirogenic solution of sodium chloride, using a syringe or intravenous injector (as for the vaccine) in volumes of 0.2 ml to 0.5 ml")

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Outcomes	Serological Paired sera taken from 198 children who developed ILI symptoms during the season to confirm an influenza diagnosis. "Antigenic activity" (presumably immunogenicity) was tested on 655 children with paired sera taken 1 month apart Effectiveness "Considering the mixed nature of the 1984 influenza epidemic and the fact that the tested preparations did not contain component B, it is interesting to analyse the rate of illness in children in the second half of the epidemic. At this time, the intensive circulation of the influenza virus type A (HINI) amongst children was confirmed by serological methods. A subsequent analysis showed that according to data from clinical diagnostics, 14.4% of children aged 11 to 14 years inoculated with the chromatographic preparation contracted influenza and acute respiratory illnesses in February to March 1984. For those inoculated with the centrifugal preparation the figure was 13.0% and for those who received placebo the figure was 12.6%. According to data from the serological correction of diagnoses, influenza A (HINI) was confirmed in 18.2% of those inoculated with the chromatographic preparation, 24.2% of those inoculated with the centrifugal preparation and 37.9% of children in the control groups. Figures for the corrected rate of illnesses were 2.6 and 3.1, as opposed to 4.8 in the control group. The indices of efficacy were 1.9 and 1.6 respectively. The differences in the figures given are statistically reliable (P < 0.001 and 0.01)" Safety "Reactogenicity was assessed on a sample of 866 school children aged 11 to 14 years. Paediatricians carried out a daily clinical examination of the children for 5 days after immunisation. This included the compulsory measuring temperatures, noting complaints of general reactions (feeling unwell, headaches, disturbed sleep etc.) and local reactions (reddening of skin, development of infiltrates, presence of illness at place of preparations' administration" The basis for the sampling is unclear and it is not at all clear whether this is a random sample DATA NOT EXTRACTED. Earlier in the report, the text reports "When the groups were formed, with the aim of evaluating the preparations' reactogenic properties and antigenic activity, the units of selection were individuals" ??? Data for the 866 children include several measures of induration and fever (Table 1) Elsewhere the text reports: "In order to evaluate the safety of the inactivated influenza vaccine, a comparative analysis was carried out of requests for emergency medical attention amongst those children who were inoculated and those who received placebo, for the 30 days after immunisation. The total figures for such requests amongst children aged 11 to 14 years and teenagers were 0.1% to 0.3% and 0.7% in the analogous group of children who had received placebo. The frequency of hospitalisation for inoculated children and those who had received placebo also did not reliably differ and did not exceed 0.04% to 0.06%". The outcomes reported in this analysis (Table 3) are very unusual ("allergies, bronchitis, neuralgia, carbuncles, stomach ulcers etc.) and there are gross imbalances and inconsistencies in the denominators of the arms (centrifugal 6625, adsorptive 491, chromatographic 4655, placebo 3493 = 15264)"
Funding Source	Unclear
Notes	The authors conclude that: 1. "The safety, low reactogenicity and high antigenic activity of the Soviet whole-virion inactivated influenza vaccine has been established, when administered once

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ab Vasil'eva 1988b (*Continued*)

	subcutaneously in a dose of 7.0 μg of haemagglutinin to school children aged 11 to 14 years and to teenagers 2. In view of the discovery of the residual reactogenicity of the adsorbitive(?) influenza chemical vaccine, it is recommended that further work should be carried out on the preparation, aiming to ensure the possibility of an intravenous method of administration 3. The clear prophylactic efficacy of the whole-virion vaccine during the mixed epidemic period of influenza B+A (HINI) was noted: the indices of efficacy, from the calculation of the serological correction of clinical diagnoses, were 1.6 and 1.9 4. The safety, high inoculation activity and prophylactic efficacy allow the inactivated influenza whole-virion vaccines to be recommended to be introduced as part of the practical prevention of health of children aged 11 years and older" We are not happy about the large number of inconsistencies in the text and non-random (or at least unexplained) sampling carried out. Terrible reporting leading to loss of data. We have tried extracting data for influenza from the effectiveness text assuming a denominator of 6596 for all vaccinees and 3393 for placebo, converting percentages from the text as follows for influenza A (H1N1) 18.2%/ of those inoculated with the chromatographic preparation (4655 i.e. 847), 24.2% of those inoculated with the centrifugal (6625) preparation and 37.9% (i.e. 1603) of children in the control groups (3393, not 3493 as it says in Table 3, i.e. 1286). As the summed denominators exceed the denominator reported . However these numerators do not match even remotely the 198 paired sera taken for influenza diagnosis. Too many inconsistencies

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not described
Summary assessments	High risk	Insufficient information to assess study design

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aa Vesikari 2006a

Methods	Double-blind RCT assessing efficacy and safety of CAIV-Trivalent in children. The trial was multicentre conducted in Belgium, Finland, UK, Israel, Spain during the period 2 Oct 2000 to 31 May 2002. Follow-up for each year lasted until 31 May and was a composite of phone calls, home and visit clinics. Coding was carried out centrally as well as randomisation and assigned by a blind investigator on the basis of a pre-printed randomisation schedule. Both ITT and PP populations were defined. Analyses were carried out only for outcomes occurring in periods of viral circulation in the different centre areas
Participants	1616 healthy children aged 6 to 35 months attending daycare (at least 12 hours weekly) in 1 of the centres who continued to be healthy during year 2 were included in the primary analysis (951 vaccine and 665 placebo recipients). Originally 1784 participants were randomised on 3:2 basis. There was considerable attrition between the year 1 ITT population (1059 in the active arm and 725 in the placebo arm) and the year 2 PP population (640 and 450 respectively), with 65 dropouts in the placebo arm and 132 in the intervention arm (calculated from the flow diagram of population which does not add up). Table 1 reports 174 of the 1616 PP population being aged 6 to 12 months, 598 12 to 23 months and 844 aged 24 months or more
Interventions	CAIV-T (Wyeth) containing A/New Caledonia/20/99 (H1N1), A/Sydney/05/97 (H3N2) and B/Yamanashi/166/98 in year 1 and A/New Caledonia/20/99 (H1N1), A/Panama/2007/99 (H3N2) and B/Victoria/504/2000 or sterile physiological solution placebo. For technical reasons, antigens in year 1 were similar to those recommended and in year 2 they were those recommend by WHO. Dose was 0.2 ml in each nostril twice in year 1 (approximately 35 days apart) and once in year 1. Spray applicators were preloaded centrally and all identical. In year 1 the match was good, in Year 2 the match was not so good because of drifted variants and the appearance of 2 different strains of influenza B vaccine
Outcomes	Serological Children with fever (rectal 38°C or more and oral 37.5°C or more), wheezing shortness of breath, pulmonary congestion, pneumonia or ear infection got a nasal swab and those with 2 or more of the following: runny nose, nasal congestion, sore throat, cough, muscle aches, chills, irritability, decreased activity or vomiting Effectiveness Influenza caused by subtypes antigenically similar to those contained in the vaccine (primary endpoint) and by those drifted from the recommended ones (secondary endpoint) • AOM (visually abnormal tympanic membrane (for colour, position and or mobility) with 1 or more of the following: fever (rectal 38°C or more and oral 37.5°C or more), earache, irritability, diarrhoea, vomiting, otorrhoea or any URI symptom. Febrile OM (with fever rectal 38°C or more and oral 37.5°C or more). Influenza associated AOM if it occurred in a child with a positive culture for influenza. Data were included only for those episodes occurring 15 days or more since vaccination or placebo administration and during a period of influenza virus isolation in each country. An episode of AOM had to take place at least 30 days since the previous one • Time off work of parent or guardian to care for the child with ILI (at least once during the study period) • Days off paid work. Days of daycare missed by ill children • At least 1 visit to ER/outpatients department because of ILI • At least 1 prescription for antibiotics because of ILI

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	• Days of antibiotic treatment because of ILI Safety Parents/guardians kept diary card to record axillary or rectal temperature, runny nose or nasal congestion, sore throat, cough, vomiting, activity level, appetite, irritability, headache, chills, muscle pain and antipyretic medication use, unscheduled physician contacts for 11 consecutive days from vaccination and throughout the study any unscheduled event that required healthcare contact or study termination. Fevers were classified as mild, moderate or severe (equal to or more than 37.5°C, 38.6°C and 40°C axillary respectively or 38°C, 39.1°C and 40°C rectally). AEs are reported in a mixture of table and text format. We have extracted the AEs for up to 11 days post-vaccination but the text reports no significant difference between those occurring within 11 days of vaccination and those occurring throughout the surveillance period. These are classed as possible, probable or definitely caused by vaccination but the definition of the association is unclear: "Lower respiratory tract illnesses reported as serious AEs from receipt of the first dose of study medication through the end of the first influenza surveillance period were also similar between treatment groups (pneumonia: 11 CAIV-T recipients and 9 placebo recipients; bronchitis: 3 CAIV-T recipients and 1 placebo recipient; bronchospasm: 2 CAIV-T recipients and 2 placebo recipients; bronchiolitis: 1 CAIV-T recipient and 2 placebo recipients) In participants 6 to 12 months of age, lower respiratory tract infections reported as serious AEs were pneumonia (2 CAIV-T recipients and 1 placebo recipient), bronchitis (2 CAIV-T recipients and 0 placebo recipients) and bronchospasm (1 CAIV-T recipient and 0 placebo recipients). Serious AEs judged to be possibly, probably, or definitely related to study vaccination were reported for 9 CAIV-T recipients (pneumonia and AOM, 2 recipients; bronchopneumonia, 2 recipients; pneumonia, 1 recipient; bronchiolitis, 1 recipient; bronchitis and AOM, 1 recipient; idiopathic thrombocytopenic purpura, 1 recipient; and fever, acute respiratory tract infection, dehydration and AOM, 1 recipient) and 5 placebo recipients (1 each for pneumonia and constipation; cough, wheeze and lung consolidation; pneumonia; idiopathic thrombocytopenic purpura; and hypersensitivity, erythema and periorbital edema). There were no statistically significant differences in serious AEs between treatment groups during the second influenza surveillance period. Six lower respiratory tract illnesses were reported, all among CAIV-T recipients (5 cases of pneumonia and 1 of bronchospasm). 2 cases of pneumonia were judged to be possibly, probably, or definitely related to study vaccination. A total of 4 participants (2 CAIV-T recipients and 2 placebo recipients) were withdrawn from the study because of AEs. No deaths occurred during the study period"
Funding Source	Industry
Notes	The authors conclude that "cold-adapted influenza vaccine-trivalent was well tolerated and effective in preventing culture-confirmed influenza illness in children as young as 6 months of age who attended day care". Formally this is a very well reported study following CONSORT guidelines. There are however numerous discrepancies in the text. Vaccine was not available until the end of Nov in year 2 and it is unclear what effect this had (immunisation was completed on 21 December, in the case of Israel this was after the beginning of viral circulation). In addition the centres went from 70 in year 1 to 62 in year 2 for unexplained reasons. A major unexplained problem is seen in table 7 (harm events reporting). 2 figures are shown for the six columns (vaccine and placebo by dose by year of the trial) representing "the number of subjects with known values"

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aa Vesikari 2006a (*Continued*)

	and then presumably the randomised denominator (which does not fit with either ITT or PP numbers). The figures show runny nose as significantly higher in dose 1 year 1 recipients and this may explain the high attrition between dose 1 year 1 and single dose year 2 (from 1021 to 631 !!!!!!!)

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Adequate
Allocation concealment (selection bias)	Low risk	Adequate
Blinding (performance bias and detection bias) All outcomes	Low risk	Adequate
Incomplete outcome data (attrition bias) All outcomes	Low risk	The proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate
Summary assessments	Low risk	Plausible bias unlikely to seriously alter the results

aa Vesikari 2006b

Methods	2001 to 2002 season data from Vesikari 2006
Participants	
Interventions	
Outcomes	
Funding Source	Industry
Notes	This second Year could be biased due to attrition

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient descriptions
Allocation concealment (selection bias)	Unclear risk	Insufficient descriptions

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aa Vesikari 2006b (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Unclear risk	Insufficient descriptions
Incomplete outcome data (attrition bias) All outcomes	High risk	The proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate
Summary assessments	High risk	Some doubts arise from attrition bias

ca Wiggs-Stayner 2006

Methods	Government-funded nurse-led prospective cohort study carried out in the US state of Indiana. The study was carried out in four "entitlement 1" schools which appear to have been populated by lower socioeconomic class children (80% to 90% were in receipt of free school lunches) evenly split between whites and blacks (table 1 reports detailed ethnic background by school). With a range of students of 264 to 392. Attendance rates were 93.9% to 95.3%
Participants	In school 1, 277 children aged from 5 years and a number of adults (teachers) up to the age of 49. The criteria for selection were lack of contraindications, lack of self-reported ongoing ILI and parental consent. 51 were "medically excluded and 143 finally had consent for and received the vaccine. In school 2 the figures were 273 "eligibles", 50 and 134. Overall coverage was 57% We make the denominators 741 children in non-vaccinated schools, out of 550 children in schools 1 and 2, 276 were vaccinated and 274 were not eligible for 1 reason or another
Interventions	Cold adapted recombinant spray vaccine (Flumist) in 2 intranasal doses or no vaccination. No content is described, degree of matching or surrounding community viral circulation
Outcomes	Effectiveness Days enrolled, days present and days absent during the study period (which is not reported)
Funding Source	Government
Notes	The authors conclude that "the 2 schools receiving FluMist increased their attendance rates from 95.3% and 93.9% to 96.1% and 95.8%. Previously, the comparison schools each had a 94.6% attendance rate; 1 fell to 94.4% and the other rose very slightly to 94.7%. The differences in self- or parent-reported influenza absences were not significant. However, the difference in days absent between individual vaccinated and non-vaccinated schools was statistically significant" Appalling reporting: no season, vaccine content or viral circulation, no outcome definition, no incidence of ILI, or definition of respiratory illness, selection bias, unclear conclusions and mixture of 2 designs (before and after comparisons mixed with prospective cohort). High risk of bias

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ca Wiggs-Stayner 2006 (*Continued*)

Risk of bias		*Risk of bias*
Bias	**Authors' judgement**	**Support for judgement**
PCS/RCS-Selection Exposed cohort	High risk	No description
PCS/RCS-Selection Non Exposed cohort	Unclear risk	Draw from different source
PCS/RCS-Comparability	Unclear risk	No description
PCS/RCS-Assessment of Oucome	Unclear risk	Not described
Summary assessments	High risk	No outcome definition, no incidence of ILI, or definition of respiratory illness, selection bias, unclear conclusions and mixture of 2 designs

ab Wright 1976a

Methods	2 studies are reported in the paper: • RCT conducted on infants to determine safety and reactogenicity of monovalent flu inactivated vaccine (Wright 1976 2) • Placebo-controlled cohort study carried out on preschool children (Wright 1976 1)
Participants	33 preschool children aged 3 to 6 were enrolled in the other study 35 children enrolled in the Paediatric Vaccine Clinic at Vanderbilt Hospital (Nashville, Tennessee) aged between 12 and 28 months
Interventions	Study participants received randomly a single dose of 0.25 ml of monovalent inactivated flu vaccine B/Hong Kong/5/72 (zonally purified, Eli Lilly and Company) containing at least 250 CCA units per dose or saline control at the time of a routine clinic visit. Vaccine or placebo were administered during a routine clinical visit. Wright 1976 1 was conducted on preschool children, participants from 1 classroom received all 1 dose of vaccine. Eight children from another classroom consisting of 12 participants received vaccine, whereas the remaining 4 were given saline solution in double-blind manner. Three of these 4 controls received 1 dose of vaccine 6 weeks later. Study participants received randomly a single dose of 0.25 ml of monovalent inactivated flu vaccine B/Hong Kong/5/72 (zonally purified, Eli Lilly and Company) containing at least 250 CCA units per dose or saline control at the time of a routine clinic visit. Vaccine or placebo were administered during a routine clinical visit
Outcomes	Serological Hemagglutinin inhibition antibody test against 4 units of Flu/B/HK/8/73 antigen Effectiveness N/A Safety

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ab Wright 1976a (*Continued*)

	Parents of the children completed a questionnaire to record local and systemic reactions so as the temperature at 20:00 on the day of vaccination. Parents were unaware if the children received immunisation
Funding Source	Industry
Notes	Parents of the children completed a questionnaire to record local and systemic reactions so as the temperature at 20:00 on the day of vaccination. Parents were unaware if the children received immunisation

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	High risk	Not used
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Single
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up
Summary assessments	High risk	Insufficient information to assess study design

ab Zangwill 2001

Methods	Randomised, placebo-controlled trial to assess safety and reactogenicity of 4 different lots of cold adapted influenza vaccine. The aim of the study was to test replicability of lots vs placebo vs a different concentration
Participants	Healthy children aged 12 to 36 months from the Kaiser Permenente paediatric clinic population. Children could be enrolled only in absence of the following conditions: hypersensitivity to eggs, presence of underlying chronic illnesses for which influenza vaccine was recommended, immunodeficiency diseases, acute febrile illnesses within 7 days or upper respiratory illnesses within 3 days of vaccination, prior receipt of inactivated flu vaccine or CAIV-T, administration of an investigational drug within 1 month of vaccination in this study, administration of any live virus vaccine within 1 month of vaccination in this study, administration of any inactivated vaccine, within 2 weeks of vaccination in the study, history of wheezing or bronchodilator medication use within 2 weeks before vaccination, receipt of any blood product within 3 months before vaccination, administration of nasal medication during the first 10 days after vaccination, no telephone in the household. 500 were enrolled

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ab Zangwill 2001 (*Continued*)

Interventions	"Subjects were randomised into five groups to receive 1 of the following preparations: • Groups 1,2,3: Cold adapted trivalent influenza vaccine containing 107,0 TCID50 of each A/Shenzhen/227/95 (H1N1), A/Wuhan/359/95 (H3N2), B/Harbin/7/94 -like viral strains • Group 4: Cold adapted trivalent influenza vaccine containing 106,7 TCID50 of A/Texas/36/91 (H1N1), A/Wuhan/359/95 (H3N2), B/Harbin/7/94- like virus strains (same lot employed in the study of Belshe 98) • Group 5: placebo of egg allantoic fluid containing sucrose-phosphate glutamate Each preparation was as intranasal spray administered in 2 doses of 0.5 ml (0.25 ml per nostril) about 60 days apart. 500 children were enrolled, 474 children received 2 doses of vaccine or placebo"
Outcomes	Serological Paired sera for antibody response assessment Effectiveness N/A Safety After vaccination, participants were observed for at least 15 minutes and families provided with digital thermometer and diary cards to record temperature and occurrence of symptoms listed in the card (lethargy , irritability, runny nose/nasal congestion, sore throat , cough, headache, muscle aches, chills, vomiting) for 10 days. Others symptoms or medications taken were also reported
Funding Source	Industry
Notes	The authors conclude that all lots of vaccines were safe and immunogenic. The number of individuals who compose each arm was not given in the paper but obtained by contact with the author

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation list
Allocation concealment (selection bias)	Low risk	Coded
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Possibly for attrition bias
Summary assessments	Low risk	Plausible bias unlikely to seriously alter the results

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aa Bracco Neto 2009a

Methods	Placebo-controlled, (year 1 = 2001) Multicentre study conducted during the 2001 and 2002 influenza seasons at 35 sites in South Africa, Brazil and Argentina (Southern Hemisphere)
Participants	3200 children 6 to 36 months of age who were in good health were enrolled. Exclusion criteria in year 1 included any 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 Live attenuated influenza vaccine (LAIV) or placebo
Interventions	LAIV versus 2 placebos: excipient or saline placebo. Saline placebo (Salplacebo) consisted of physiologic saline; excipient placebo (Eccplacebo) was the vaccine excipient alone (sucrose-phosphate-glutamate buffer, arginine, acid hydrolyzed porcine gelatin and normal allantoic fluid), in the same concentration as in LAIV. There were four arms in Year1: LAIV 2 doses, Eccplacebo, Salplaceboand LAIV 1 dose plus SalPlacebo 1 dose each. Vaccine content and degree of vaccine matching were unclear
Outcomes	Laboratory Culture "standard techniques by laboratories in Argentina, Brazil and South Africa" Effectiveness Cultured-confirmed influenza illness and all episodes of AOM and any LRTI, hospitalisation Safety Reactogenicity events and AEs
Funding Source	Industry
Notes	The authors conclude "that a single dose of LAIV provided clinically significant protection against influenza in young children previously UV against influenza and 2 doses provided persistent protection through a second season without revaccination. These benefits, together with the vaccine's safety profile in children 2 years of age and older, provide support for increased use of LAIV in children < 2 years of age. LAIV was well tolerated; no significant differences in solicited reactogenicity events were seen between treatment groups. LAIV was not associated with an increased rate of AEs through day 11 postvaccination. When AEs were assessed through day 28 postvaccination in year 2, the rate of bronchitis was significantly increased in LAIV recipients, although rates of bronchospasm and any respiratory AEs were similar between groups. Additionally, no differences in solicited reactogenicity events or other AEs were seen after either saline or excipient placebo. This suggests that the excipients in LAIV, which include egg protein and acid-hydrolyzed gelatin, do not contribute to reactogenicity in vaccine recipients" The description of trial methods and results is unclear. The rationale for the use of 2 placebos is unclear. An allocation mistake was made in Year 2 of the study with a swap of a group from active to placebo and vice versa. It is unclear whether blinding was maintained throughout or not but attrition appears to have gone up to 58% (Figure 1 is very difficult to interpret). In addition numerators are not reported and there is no mention of attempts at standardisation of laboratory procedures across 2 continents and

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aa Bracco Neto 2009a (*Continued*)

	three states

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random lists
Allocation concealment (selection bias)	Low risk	Centralised randomisation scheme
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Few losses to follow-up
Summary assessments	Low risk	Plausible bias unlikely to seriously alter the results

ba Cochran 2010a

Methods	Case-control study to assess influenza vaccine effectiveness among children aged 6 to 23 months within the Northern California Kaiser Permanente Medical Care Program who tested positive for influenza during the years 2003-2006
Participants	Description of cases: children aged 6 to 23 months whose families were enrolled in Kaiser Permanente Northern California (KPNC) membership who tested positive for influenza during the years 2003-2006 Description of controls: participants without a positive influenza test were matched to each of these cases based on birth month/year and zip code
Interventions	1 and 2 doses of the trivalent inactivated vaccine against laboratory-confirmed influenza
Outcomes	
Funding Source	Government
Notes	The authors conclude that "during the 2005-2006 influenza season, when predominant circulating virus strains and vaccine strains were well-matched, vaccination was 76% (95% CI: 37% to 91%) effective against laboratory-confirmed infection. There was no statistically significant effect of vaccination, however, for the 2003-2004 or 2004-2005 seasons. Our results highlight the need for further study of influenza vaccine effectiveness in this age group" A very strangely reported study with Results before Methods (pages are numbered consecutively, though) . Unclear case selection process and no mention of blind exposure assessment. No data were available on symptom status of cases or controls

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ba Cochran 2010a (*Continued*)

Risk of bias		*Risk of bias*
Bias	**Authors' judgement**	**Support for judgement**
CC-Case Selection	High risk	Not clearly described
CC-Control Selection	Unclear risk	Apparently same population
CC-Comparability	High risk	Insufficient description
CC-Exposure	Low risk	Secure record
Summary assessments	High risk	Lack of information about study design and matching method

ba Eisenberg 2008a

Methods	A prospective, population-based case-control study of hospitalisations attributable to laboratory-confirmed influenza was performed in counties that encompass Nashville, Tennessee, Rochester, New York and Cincinnati, Ohio, during the 2003-2004 and 2004-2005 influenza seasons. Each site conducted surveillance at sufficient hospitals to capture 95% of hospitalisations attributable to acute respiratory illness (ARI) or fever among children residing in the respective county. Study nurses enrolled children within 48 hours after admission to surveillance hospitals Sunday through Thursday in the 2003-2004 influenza season and 7 days per week during the 2004-2005 season
Participants	Description of cases: Eligible children were county residents, 5 years of age or younger, with an admission diagnosis of ARI or fever with laboratory-confirmed influenza Description of controls: Children resident in the same county of cases who tested negative for influenza were control participants
Interventions	Unclear. Matching is described as suboptimal
Outcomes	
Funding Source	Government
Notes	The authors conclude that "even in an influenza season (2004-2005) with a suboptimal vaccine match, more than 1 half of these visits could be prevented with recommended influenza vaccination Partial vaccination did not seem to be effective These results offer additional evidence in support of recommendations for vaccinating children against influenza and they highlight the importance of children receiving the recommended number of influenza vaccinations" • No mention of blind exposure assessment is made and effects of vaccine on laboratory outcomes supposedly assesses effectiveness • No broken down data are provided

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ba Eisenberg 2008a (*Continued*)

Risk of bias		*Risk of bias*
Bias	**Authors' judgement**	**Support for judgement**
CC-Case Selection	Low risk	Independent validation
CC-Control Selection	Low risk	Same population
CC-Comparability	Low risk	Possibly adequate
CC-Exposure	Low risk	Secure record
Summary assessments	Low risk	Plausible bias unlikely to seriously alter the results

ba Gilca 2011

Methods	Matched case-control study performed to assess the effectiveness of a single paediatric dose of AS03-adjuvanted vaccine (Pandemrix, GSK) against hospitalisation in children aged 6 months to 9 years during the fall 2009 vaccination campaign in Quebec, Canada
Participants	Participants • Description of cases: children hospitalised for PCR-confirmed pH1N1 infection ("Quebec residents aged 6 months to 9 years hospitalised with laboratory-confirmed pH1N1 infection") • Description of controls: non-hospitalised children, matched by age and region of residence. For each case, 15 potential controls were selected at random from the health insurance registry
Interventions	A single paediatric dose of AS03-adjuvanted pH1N1 vaccine vs. no intervention
Outcomes	
Funding Source	Government
Notes	The authors conclude that a single paediatric dose of the AS03-adjuvanted pH1N1 vaccine given to children aged 6 months to 9 years is highly protective against hospitalisation, beginning as early as 10 days after immunisation. The study is summarily reported. It is unclear whether blinded assessment of exposure status was carried out. In addition it is unclear whether the children were hospitalised because of influenza or whether influenza was a chance finding and hospitalisation took place because of other reasons. This is a very important aspect in pandemic H1N1 infection where most of deaths were recorded for multiple pathologies

Risk of bias		*Risk of bias*
Bias	**Authors' judgement**	**Support for judgement**
CC-Case Selection	Low risk	Independent validation
CC-Control Selection	Low risk	Community control

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ba Gilca 2011 (*Continued*)

CC-Comparability	Unclear risk	Drawn from insurance registry
CC-Exposure	Unclear risk	Self-reported
Summary assessments	Unclear risk	Plausible bias that raises some doubt about the results

ba Kelly 2011

Methods	Case-control study (The Western Australian Influenza Vaccine Effectiveness, WAIVE), evaluating protective effect of inactivated influenza vaccination in children aged 6 to 59 months, by means of a prospective case-control study conducted in general practices and a hospital emergency department. Eligible patients were tested for influenza and a range of other common respiratory viruses • Influenza vaccine effectiveness (VE) against laboratory-confirmed influenza was estimated with cases defined as children with an ILI who tested positive and controls as those with an ILI who tested negative for influenza virus
Participants	Participants were children aged 6 to 59 months presenting with an ILI and from whom swabs had been taken for laboratory testing ILI definition used in this study was: "documented fever with oral (or aural) temperature 38°C (or axillary temperature 37.5°C), with at least 1 acute respiratory symptom or sign. Children were recruited if they had met the case definition for an ILI within the previous 72 hours" All emergency department participants were recruited from the Emergency Department of Princess Margaret Hospital for Children, the only paediatric tertiary hospital in WA. Children were also recruited from general practices in metropolitan Perth and Kalgoorlie Description of cases: Those testing positive for influenza viruses were identified as cases Description of controls: While those testing negative for influenza viruses were identified as controls Cases and controls were recruited when they presented with an ILI but their case or control status was not known at the time
Interventions	Informed consent was obtained, parents were provided with a questionnaire to complete, which included demographic data, influenza vaccinations received in 2008 and previous years and any underlying chronic illnesses. Vaccine status was validated for 87% of all participants with the vaccine provider of the child • Children were defined as FV if they had received 2 age-appropriate doses of vaccine at least 21 days apart and more than 14 days before ILI onset in 2008 • Children were also defined as FV if they had received at least 2 previous doses of influenza vaccine in any year and 1 dose of the age-appropriate vaccine in 2008. Children who received no vaccine in 2008 were counted as UV and all other children were defined as partially vaccinated
Outcomes	Laboratory "All samples were then tested by real-time PCR directed to specific targets in the matrix genes of influenza A and B and the H1 and H3 genes of influenza A.13,14 Samples were also cultured for influenza viruses using centrifuge-enhanced inoculation of Madin-Darby canine kidney cells and those which were culture

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ba Kelly 2011 (*Continued*)

	positive were referred to the World Health Organization Collaborating Centre for Reference and Research on Influenza in Melbourne, where detailed antigenic characterisation was performed. In addition to influenza viruses, the swabs were tested by PCR for the presence of rhinoviruses, respiratory syncytial viruses, parainfluenza virus types 1, 2 and 3, human metapneumoviruses and enteroviruses. Viral culture for adenoviruses was also performed using diploid lung fibroblast cells and monitoring for cytopathic effect"
Funding Source	Government
Notes	The authors conclude that "A total of 75 children were enrolled from general practices and 214 through the emergency department, with 12 (27%) and 36 (17%), respectively, having laboratory-confirmed influenza. Using all the influenza negative controls, the adjusted VE was 58% (95% confidence interval, 9-81). When controls were limited to those with another virus present, the adjusted VE was 68% (95% confidence interval, 26-86). VE estimates were higher when controls included only those children with another respiratory virus detected" • A well-reported and well conducted study, the only concern is about the role of confounding variables selected to adjust estimates

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
CC-Case Selection	Low risk	Independent validation
CC-Control Selection	Low risk	Drawn from the same population - hospital control
CC-Comparability	Unclear risk	Adjustment by confounders
CC-Exposure	Low risk	Secure record - interview
Summary assessments	Unclear risk	Plausible bias that raises some doubt about the results

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ba Kissling 2011

Methods	Third season of I-MOVE (Influenza Monitoring Vaccine Effectiveness in Europe), multicentre, case-control study based on sentinel practitioner surveillance networks in eight European Union (EU) member states to estimate 2010/11 influenza vaccine effectiveness (VE) against medically-attended ILI laboratory-confirmed as influenza The 8 study sites included in the multicentre, case-control study were settings in France, Hungary, Ireland, Italy, Poland, Portugal, Romania and Spain. In six study sites, primary care practitioners belonging to the national influenza sentinel networks were invited to participate in the study. In Portugal and Italy, practitioners other than those participating in the national influenza sentinel networks were also invited to participate The study population consisted of non-institutionalised patients consulting a participating practitioner for ILI or ARI (France only) who had a nasal or throat swab taken less than eight days after symptom onset and with no contraindication for influenza vaccination. In Hungary the study population was restricted to those 18 years or older. We defined the start of the study period in each of the study sites as more than 14 days after the start of the 2010 to 11 influenza vaccination campaign Practitioners in Ireland, Poland Portugal, Spain and France swabbed all ILI/ARI patients aged 65 and over, in Hungary they swabbed all ILI patients 60 and over and in Italy they systematically swabbed 1 ILI/ARI patient aged 65 and over per week. In all study sites practitioners systematically sampled ILI/ARI patients to swab among the other age groups, apart from Romania where practitioners swabbed all ILI patients in all age groups In all study sites, practitioners interviewed the ILI patients using country-specific questionnaires. The common variables collected in the eight study sites included ILI signs and symptoms, age, sex, pregnancy, presence of chronic conditions, severity of the chronic disease measured as the number of hospitalisations for the chronic disease in the previous 12 months, smoking history (none, past, current smoker), number of practitioner visits in the previous 12 months, 2009 to 10 pandemic vaccination status, seasonal influenza vaccination in the 2009 to 10 and in the 2010 to 11 season ILI patient were excluded if they presented ILI symptoms before the week of onset of the first recruited influenza case. For each study site, ILI patients were excluded if presenting either after the onset week of the last recruited influenza case or after the onset week of the case prior to 2 consecutive weeks of no positive case recruited To estimate VE against A(H1N1)2009 and against influenza B virus, we based the exclusion criteria on the week of onset of the first and last A(H1N1)2009 and influenza B case respectively
Participants	Description of cases A case was defined as a patient with signs and symptoms adhering to the EU ILI case definition (sudden onset of symptoms and at least 1 of the following four systemic symptoms: fever or feverishness, malaise, headache, myalgia and at least 1 of the following three respiratory symptoms: cough, sore throat, shortness of breath), who was swabbed and tested positive for influenza using real-time polymerase chain reaction (qRT-PCR) or culture Description of controls Controls were EU ILI patients who were swabbed and tested negative for influenza
Interventions	An individual was considered vaccinated if he/she received at least 1 dose of the 2010 to 11 seasonal vaccine more than 14 days before the date of onset of ILI symptoms

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ba Kissling 2011 (*Continued*)

Outcomes	Laboratory Those who were swabbed and tested positive for influenza using qRT-PCR or culture. Swabs were tested for influenza at the respective countries' National Influenza Reference Laboratory (in Spain, the laboratories of the regional sentinel networks integrated in the Spanish Influenza Sentinel Surveillance System). In each country, all or a subset of influenza isolates were antigenically characterised. Laboratory viral detection, typing, subtyping and variant analysis performed in each of the National Reference Laboratories are described elsewhere (European Centre for Disease Prevention and Control (ECDC) (2010) European Influenza Surveillance Network (EISN). Table 2: Characteristics of the virological surveillance systems participating in EISN, Available from: http:// www.ecdc.europa.eu/en/activities/surveillance/EISN/laboratory˙network/ages/laboratory_network.aspx. Accessed October 2011)
Funding Source	Government
Notes	In conclusion, the I-MOVE multicentre case-control study provided summary influenza VE estimates across Europe and showed a moderate VE against medically attended ILI laboratory-confirmed influenza in a season of good match between the circulating influenza strains and the strains included in the 2010 to 11 trivalent vaccine. Next season further study sites may be included in the pooled analysis and current study sites will focus on increasing sample size through recruitment of more GPs in order to obtain more precise estimates, to carry out an adjusted 2-stage pooled analysis and to obtain age-specific estimates by influenza type among the target group for vaccination. Even if the trivalent inactivated influenza vaccines may only provide a moderate protection against medically-attended ILI laboratory-confirmed as influenza, they remain, until more efficient vaccines are available, the most effective measure to prevent influenza infection and its consequences • Well conducted and reported case-control study

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
CC-Case Selection	Low risk	Independent validation
CC-Control Selection	Low risk	Drawn from the same population
CC-Comparability	Low risk	Study controls for age group, sex, presence of chronic conditions, at least 1 hospitalisation in the previous 12 months for chronic disease, smoking history, number of practitioner visits in the previous 12 months
CC-Exposure	Low risk	Secure record
Summary assessments	Low risk	Possible under-estimation

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ba Mahmud 2011

Methods	Pandemic vaccines: population based case-control study. Assessing the effectiveness of the pandemic H1N1 and seasonal trivalent influenza vaccines (TIV) used during the 2009 mass vaccination campaign in Manitoba (Canada) in preventing laboratory-confirmed H1N1 infections. Study uses data from Cadham Provincial Laboratory (CPL) and the Manitoba Immunization Monitoring System (MIMS). All Manitoba residents ≥ 6 months of age who had a respiratory specimen tested at CPL for H1N1 were included in the study
Participants	Any adult or child ≥ 6 months of age who normally resides in Manitoba and who had a respiratory sample submitted to CPL for influenza testing during the study period was eligible for inclusion in the study. The study was conducted from November 2, 2009 (1 week after the start of mass vaccination in Manitoba) to February 10, 2010 Description of cases Cases were individuals who tested positive for pandemic H1N1 influenza A by reverse transcriptase-PCR (RT-PCR). RT-PCR assay developed by the National Microbiology Laboratory Description of controls Controls were individuals who tested negative for both influenza A and B. Information on receipt of TIV or H1N1 vaccine was obtained by record linkage with MIMS, the population-based province-wide immunisation registry. The date of specimen collection was considered the 'index date' Exclusion criteria 12 individuals were excluded because they tested positive for influenza A but not for H1N1
Interventions	For all cases and controls, information on the receipt of the pandemic H1N1, TIV and the polyvalent pneumococcal polysaccharide (PPV23) vaccines during or before the 2009/10 season was obtained from MIMS, the population-based province-wide registry recording virtually all immunisations administered to Manitoba residents since 1988. Estimates of the completeness and accuracy of the recorded vaccination information are high. Vaccinated individuals were classified into three groups depending on whether vaccination occurred 1-6, 7-13, or ≥ 14 days before the index date
Outcomes	Laboratory-confirmed influenza
Funding Source	Government
Notes	The authors conclude that "Overall, we found that the adjuvanted H1N1 vaccine was 86% effective in preventing laboratory-confirmed H1N1 infections when received ≥ 14 days before testing, although effectiveness seemed lower among persons aged ≥ 50 years (51%) and among those with immunocompromising conditions (67%). We demonstrated that the adjuvanted H1N1 vaccine used during Manitoba's mass vaccination campaign was highly effective against laboratory-confirmed H1N1 infections, especially among children and younger adults. Despite logistical and communication challenges to vaccine delivery during the campaign, vaccine effectiveness appears comparable to that observed for influenza vaccines during non-pandemic seasons in years with good antigenic match. This study demonstrates the utility of laboratory information systems and administrative databases for evaluating the effectiveness of influenza vaccines" • A well conducted and reported case-control study

Risk of bias			***Risk of bias***
Bias	**Authors' judgement**	**Support for judgement**	

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ba Mahmud 2011 (*Continued*)

CC-Case Selection	Low risk	Record linkage
CC-Control Selection	Low risk	Drawn from the same population
CC-Comparability	Low risk	Adjustment by confounding factors
CC-Exposure	Low risk	Secure record
Summary assessments	Low risk	Plausible bias unlikely to seriously alter the results

ab Mallory 2010

Methods	Randomised, placebo controlled trial carried out on children aged between 2 and 17 years in order to assess safety, tolerability, and immunogenicity of a monovalent intranasal 2009 A/H1N1 live attenuated influenza vaccine (LAIV, MedImmuine)
Participants	Inclusion criteria 1. Male or female, aged 2 to 17 years 2. Healthy by medical history and physical exam 3. Written informed consent and any locally required authorisation (e.g. HIPAA in the USA, EU Data Privacy Directive in the EU and written informed assent) obtained from the subject or their legal representative before performing any protocol-related procedures, including screening evaluations 4. Subject or their legal representative available by telephone 5. Subject or subject's legal representative is able to understand and comply with the requirements of the protocol, as judged by the investigator 6. Ability to complete follow-up period of 180 days after dose 2 as required by the protocol Exclusion criteria 1. History of hypersensitivity to any component of the investigational product including egg or egg protein, gelatin or arginine, or serious, life-threatening, or severe reactions to previous influenza vaccinations 2. History of hypersensitivity to gentamicin 3. Any condition for which the inactivated influenza vaccine is indicated, including chronic disorders of the pulmonary or cardiovascular systems (e.g., asthma), chronic metabolic diseases (e.g., diabetes mellitus), renal dysfunction, or haemoglobinopathies that required regular medical follow-up or hospitalisation during the preceding year 4. Acute febrile (> 100.0°F oral or equivalent) and/or clinically significant respiratory illness (e.g. cough or sore throat) within 14 days before randomisation 5. History of asthma, or history of recurrent wheezing in children aged < 5 years 6. Any known immunosuppressive condition or immune deficiency disease, including HIV infection, or ongoing immunosuppressive therapy 7. History of Guillain-Barré syndrome 8. A household contact who is severely immunocompromised (e.g. hematopoietic stem cell transplant recipient, during those periods in which the immunocompromised individual requires care in a protective environment); subject should additionally avoid

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	close contact with severely immunocompromised individuals for at least 21 days after receipt of investigational product 9. Receipt of any investigational agent within 30 days before randomisation, or expected receipt through 30 days after the second dose of investigational product (use of licensed agents for indications not listed in the package insert is permitted) 10. Use of aspirin or salicylate-containing products in children within 30 days before randomisation or expected receipt through 30 days after final vaccination 11. Expected receipt of antipyretic or analgesic medication (non-salicylate-containing) on a daily or every other day basis from randomisation through 14 days after receipt of each dose of investigational product 12. Administration of intranasal medications within 14 days before randomisation, or expected receipt through 14 days after administration of each dose of investigational product 13. Receipt of any non-study vaccine within 30 days before or after dose 1 or expected receipt of any non-study vaccine within 30 days before or after dose 2 14. Known or suspected mitochondrial encephalomyopathy 15. Any condition (e.g. chronic cough, allergic rhinitis) that, in the opinion of the investigator, would interfere with evaluation of the investigational product or interpretation of subject safety or study results 16. Subject, legal representative, or immediate family member of subject is an employee of the clinical study site or is otherwise involved with the conduct of the study
Interventions	H1N1 LAIV (2009 formulation) by MedImmune and was derived by genetic reassortment of the hemagglutinin and neuraminidase genes from the wild-type A/California/7/2009 virus and the remaining 6 gene segments from an attenuated master donor virus. The resulting 6:2 reassortant vaccine virus is grown in chicken eggs using the same manufacturing process used to produce MedImmune's seasonal trivalent LAIV • *Monovalent vaccine* was supplied in intranasal spray applicators containing approximately 107 fluorescent focus units (FFU) of the reassortant influenza virus in a total volume of 0.5 mL of sucrose-phosphate buffer and egg allantoic fluid (0.25 mL administered into each nostril) • *Placebo* (0.5 mL of sucrose-phosphate buffer) was supplied and administered using identical intranasal applicators Eligible subjects were randomly assigned using an interactive voice response system in a 4:1 ratio to receive 2 doses of live monovalent H1N1 LAIV or placebo by intranasal spray 28 days apart. Randomisation was stratified by age (2 to 8 years and 9 to 17 years) Initially 326 children were enrolled and 261 (133 between 2 and 8 years and 128 between 9 and 17 years) were allocated to vaccine group, whereas 65 (29 between 2 and 8 years and 36 between 9 and 17 years) were allocated to control placebo Study subjects were further randomised (1:1) to provide a blood sample on either day 15 or day 29 after their first vaccination. A final immunogenicity blood sample was collected on day 57, approximately 28 days after the second vaccination. After the blinded portion of the study was concluded, subjects randomised to receive placebo in the studies were offered optional H1N1 vaccination after collection of their Day 57 blood sample

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Outcomes	Laboratory Serum antibody titers were measured at baseline and on day 15 or 29 after dose 1 and on day 57 (28 days after dose 2) using a standardised hemagglutination inhibition (HAI) assay against antigenically matched influenza A/H1N1 6:2 virus reassortants Safety A) The primary safety analysis compared the rates of fever (defined as a temperature of at least 38.3°C) during days 1 to 8 after dose 1 B) Additional safety endpoints (from day 1 through day 8 and from day 1 through day 15 after each vaccination) included: • *Solicited symptoms*: fever (temperature was recorded daily), runny/stuffy nose, sore throat, cough, muscle aches, decreased activity, decreased appetite, and headache • *AEs*: blood and lymphatic system disorders, ear and labyrinth disorders, eye disorders, gastrointestinal disorders, general disorders and administration site conditions, immune system disorders, infections and infestations, injury poisoning and procedural complications, musculoskeletal and connective tissue disorders, nervous system disorders, respiratory thoracic and mediastinal disorders, skin and subcutaneous tissue disorders • *Antipyretic and analgesic use*. In any case their use was discouraged during the 14 days postvaccination to avoid masking the primary safety endpoint of fever Memory aid worksheets were provided to record solicited symptoms, AEs, and concomitant medication use for 14 days after dosing C) SAEs and new onset chronic diseases (NOCDs) were collected through 180 days after the final dose Subjects who experienced a febrile illness within 7 days after dose 1 were instructed to return to the study site for evaluation
Funding Source	Industry (MedImmune)
Notes	The authors conclude that "This study demonstrates that 2 doses of 2009 H1N1 LAIV are safe in healthy children. Overall, the frequency of solicited symptoms and AEs were similar between H1N1 LAIV and placebo recipients, and most were mild to moderate in severity"

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random list
Allocation concealment (selection bias)	Low risk	Centralised

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ab Mallory 2010 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Few losses to follow-up
Summary assessments	Low risk	

ca Ortqvist 2011

Methods	Prospective cohort study carried out on Stockholm Country inhabitants aged at least 6 months between week 44 and 52 in order to assess effectiveness of pandemic monovalent flu vaccine H1N1 (Pandremix by GSK) in preventing laboratory-confirmed H1N1 flu cases. Estimates were calculated by linking data from different database: Sminet (for laboratory-confirmed H1N1 flu cases), Vaccinera (on which data of vaccinated participants has been reported), Common Health-Care Registers for Stockholm Country Council (GVR, for detect hospital admission cases due to Influenza H1N1), Statistic Sweden (for demographical data)
Participants	Inhabitants of Stockholm country (2,019,183 out of which 449,971 were aged under 19 years)
Interventions	• Pandemrix (GSK), split virion, inactivated, monovalent AS03-adjuvanted vaccine • A dose (0.5 mL) contained 3.75 lg of an influenza A/California/7/ 2009 (H1N1)v-like strain and an adjuvant composed of squalene, DL-a-tocopherol and polysorbate 80 • 2 doses of 0.5 ml (participants aged at least 13 years) or of 0.25 ml (between 3 and 12 years) were administered. Only participants who belong to at risk categories (i.e. diabetes mellitus or pulmonary, heart, liver, renal and immunocompromising disease) were initially recommended for vaccination in the 6 months to 3 years age class, from week 46 onwards this was extended to the whole age class Immunisation campaign started in week 42. Data about vaccination are recorded in the "Vaccinera" database where date of vaccination, batch number of the vaccine, the person's unique identification number, medical risk group of vaccinated are reported). A flu case was considered vaccinated if diagnosis/hospital admittance occurred more than 14 days after administration of the 1st vaccine dose. Twenty- five cases of confirmed H1N1 flu cases had been observed between weeks 44 and 52 among participants who received 1 or 2 vaccine doses at least 14 days before diagnosis or hospitalisation. Out of them 11 (10) were aged between 6 months and 12 years
Outcomes	Laboratory Not assessed Effectiveness Cases of laboratory-confirmed H1N1 flu cases notified to the Institute for Infectious Diseases Control and available in the "Sminet" database, occurred between week 42 and 52 of 2009. Incidence rate ratios for a given week were calculated comparing the rate of persons who

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ca Ortqvist 2011 (*Continued*)

	developed influenza > 14 days after being vaccinated out of the cumulated number of persons who had been vaccinated up until 2 weeks before with the rate of persons with an influenza diagnosis out of all non-vaccinated persons, excluding persons who had had a previous influenza diagnosis Safety Not assessed
Funding Source	Government Funding was provided by the County Council of Stockholm and by the Department of Communicable Diseases Control and Prevention, Stockholm County. Authors declare that they have no conflicts of interest
Notes	Authors attempted to identify possible risk factors associated with vaccine failure in the study population analysing incidence of several chronic conditions in cases (total cases of vaccine failures, n = 25) and in vaccinated controls (matched for age and vaccination date) using a case-control design. For both chronic renal or hepatic disease and immuno-compromised condition a significant association was found (whole populations) As authors self-note in the discussion, "the sampling for the sampling for an influenza diagnosis was not made systematically but in routine medical care" The authors conclude that "monovalent AS03-adjuvanted influenza A(H1N1)v vaccine was very effective in preventing the pandemic influenza in Stockholm County"

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
PCS/RCS-Selection Exposed cohort	Unclear risk	Voluntary vaccinee
PCS/RCS-Selection Non Exposed cohort	Unclear risk	Refuse the vaccination
PCS/RCS-Comparability	High risk	Insufficient description
PCS/RCS-Assessment of Oucome	Low risk	Secure record
Summary assessments	High risk	Insufficient description how exposed and not exposed was selected - possible bias by indication

ab Plennevaux 2011

Methods	Randomised, placebo controlled trial assessing reactogenicity and immunogenicity of a split virion monovalent administered in children aged between 6 months and 9 years of age
Participants	A total of 474 children were enrolled in the study, 229 of them were aged 6 to 35 months, and 245 between 3 and 9 years Exclusion criteria

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	Known or suspected influenza infection since March 2009; any vaccination in the previous 4 weeks or planned within 6 weeks following the first trial vaccination; hypersensitivity to any vaccine component or life threatening reaction to a vaccine containing the same substances; known or suspected immunodeficiency; recent history (< 6 months) of immunosuppressive therapy or long-term systemic corticosteroid therapy; known HIV, hepatitis B or C infection; receipt of blood or blood-derived products in the previous 3 months, and febrile or acute illness on the day of enrolment
Interventions	Used vaccine was an inactivated split-virion preparation of the New York Medical College (NYMC) X-179A reassortant of the A/California/07/2009 (H1N1) strain and the PR8/8/34 strain, distributed by the US Centers for Disease Control and Prevention (CDC). Seed virus was propagated in embryonated chicken eggs, inactivated and split according to the process used to produce a seasonal influenza vaccine licensed in the US for persons aged > 6 months (Fluzone®, sanofi pasteur, Swiftwater, PA). 2 different antigenic concentrations were tested: 7.5 mcg or 15 mcg hemagglutinin (HA) per dose. Vaccine was supplied as single-dose vials without preservative for 6 to 35 month-olds and multi-dose vials containing 0.01% thimerosal preservative for 3 to 9 year-olds Children were randomly assigned to 1 of three study groups (7.5 mcg HA, 15 mcg HA, placebo) using randomisation lists with stratification by age group (6 to 35 months and 3 to 9 years). 2 doses 21 days apart were administered
Outcomes	On serum samples collected at baseline and 21 days after each inoculation, hemagglutination inhibition (HI) antibody titration against the vaccine strain using the standard HI assay with turkey erythrocytes had been performed. Immunogenicity data were summarised using geometric mean titre (GMT), geometric mean titre ratio (GMTR) , seroprotection rate (defined as % of subjects with titers ≥ 1: 40), seroconversion rate (defined as % of subjects with a pre-vaccination titre < 1:10 and a post-vaccination titre ≥ 1:40, or with a pre-vaccination titre ≥ 1:10 and ≥ 4-fold increase after vaccination) • The following solicited site reactions were noted by parents or legal guardians on safety diaries every day for 7 days after each injection together with body temperature: • ○ Local reactions: pain (children ≥ 2 years) or tenderness (children < 2 years), erythema, swelling, induration or ecchymosis ○ Systemic reactions: fever, headache, malaise, myalgia and shivering (children≥2 years) or fever, vomiting, abnormal crying, drowsiness, loss of appetite, and irritability (children < 2 years) • Grade 3 reactions were defined as: ○ pain: incapacitating, preventing usual activities ○ tenderness: infant cries when injected limb is moved/reduced limb movement; erythema ○ swelling, induration or ecchymosis ≥ 5 cm ○ fever > 39.5°C/103.1°F for infants aged 6 to 23 months, or >39.0°C/102.1°F for children aged 2 to 9 years ○ vomiting ≥ 6 episodes/24 hours or parenteral hydration required ○ abnormal crying > 3 hours ○ drowsiness: sleeping most of the time/difficult to wake up ○ loss of appetite: refused ≥ 3 meals or refused most meals ○ irritability: infant inconsolable ○ headache, malaise, myalgia or shivering: significant, prevents daily activities • Unsolicited AEs occurring within 21 days after each vaccination were also

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ab Plennevaux 2011 (*Continued*)

	recorded in the subject diaries and were judged to be either related or unrelated to vaccination by the investigator • AEs judged by the investigator to be a new onset of a chronic illness (NOCI) were to be reported separately. SAE, including AEs of special interest (i.e. anaphylaxis, Guillain-Barré syndrome, Bell's palsy, optic neuritis, convulsions or syncope) were reported throughout the study (until Day 2011 after first vaccination) using the standard procedure of immediate initial notification and follow-up reporting
Funding Source	Industry
Notes	The authors conclude that the safety and reactogenicity of the pandemic (H1N1) 2009 vaccine, at either dose, were acceptable and similar to placebo after both the first and second vaccinations. The safety results observed were similar to those seen historically with seasonal inactivated trivalent influenza vaccines

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Adequate
Allocation concealment (selection bias)	Low risk	Adequate
Blinding (performance bias and detection bias) All outcomes	Low risk	Double
Incomplete outcome data (attrition bias) All outcomes	Low risk	Few losses to follow-up
Summary assessments	Low risk	

ba Staat 2011a

Methods	Case-control study assessing the efficacy of the trivalent inactivated influenza vaccine against laboratory-confirmed influenza for the 2005-2006 and 2006-2007 influenza seasons. Vaccination rates among children 6 to 59 months of age with ARI or fever and laboratory-confirmed influenza were compared with influenza test-negative controls who also had a medically attended ARI. The design is based on active surveillance system in which the influenza vaccination status of children with laboratory-confirmed influenza was compared with that of laboratory-confirmed influenza-negative matched controls
Participants	Inpatient Children were enrolled five days a week after admission to surveillance hospitals. Eligible children were county residents, younger than five years of age, who were admitted with signs or symptoms of ARI Children were excluded if they had fever and neutropenia associated with chemotherapy, were hospitalised in the prior 4 days, transferred from another surveillance hospital, or were newborns never discharged from the hospital

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	Outpatient settings Prospective surveillance of county children presenting with ARI to selected clinics and EDs was conducted during the 2 seasons. Study personnel enrolled children in the clinics and the EDs on specified surveillance days using similar inclusion and exclusion criteria to inpatient enrolment. Children were enrolled 1 or 2 days per week in one to four paediatric clinics per county and were enrolled three or four days per week in the EDs Description of Cases and Controls Children whose specimens tested positive for influenza were eligible to be cases and those who tested negative were eligible to be controls To ensure that all children included in this study were eligible for vaccination based on current recommendations, the following parameters were used. Since the minimum age to receive a primary influenza vaccination is 24 weeks (168 days), followed by a second vaccination a minimum of 24 days later (192 days) and the child is considered protected 2 weeks following the final dose (206 days), 206 days was used as the lower age limit for this study The upper age limit was 59 months at the onset of symptoms. The onset of the child's symptoms must have occurred during influenza season for each geographic site. The start of the influenza season was defined as the occurrence of 1 or more positive influenza specimens in 2 consecutive weeks through local research or hospital laboratories at each site. The end of the influenza season was defined as the absence of 1 or more positive specimen(s) of influenza in 2 consecutive weeks Control children were matched to case children by disease onset date (plus or minus 7 days), clinical setting (inpatient, ED or clinic), geographic site (Nashville, Cincinnati, Rochester) and age (6 to 23 months, 24 to 59 months). The number of matched controls per case varied from 1 to 4 [1 control (28%), 2 controls (15%) , three controls (12%) and four controls (34%)]. For 18 children, 8 from the ED and 10 from outpatient practices, only 1 control that matched 2 cases was available, so both cases were matched to the same control
Interventions	Exposure Influenza vaccination status at the time of the ARI visit was determined through a telephone call or fax to the child's primary care practice and subsequent extraction of influenza vaccination data from the child's primary care medical record and/or, if available, the state immunisation registry. Children were classified as FV if vaccinated according to ACIP guidelines which included either 2 doses in the current season administered $\geq$ 24 days apart, or at least 1 vaccine dose in a previous influenza season and 1 dose in the current season, administered $\geq$ 14 days before ARI onset. Children were classified as being partially vaccinated if they received only 1 of the 2 recommended doses in the current season, $\geq$ 14 days before ARI onset or 2 vaccinations in the current season with the second dose administered within 14 days of the onset of ARI or < 24 days after the first dose. Children were classified as UV if they received no influenza vaccine doses during the study season or received the first of 2 recommended doses within 14 days before ARI onset during the study season
Outcomes	Laboratory Nasal and throat swabs obtained from each enrolled child were tested for influenza at each site's research laboratory with standardisation of assays across sites using reverse transcription-polymerase chain reaction (RT-PCR) assays, as described previously. A subset of children had viral cultures done. A specimen was defined as being influenza-positive if viral culture or duplicate PCR assays were positive for influenza A or B. There were no children with a positive culture for influenza and a negative PCR, while 9 children with a

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ba Staat 2011a (*Continued*)

	negative culture had a positive PCR for influenza
Funding Source	Government
Notes	The authors conclude that "Each year, young children experience high rates of hospitalizations, ED visits and outpatient visits due to influenza. We found that full vaccination with the trivalent inactivated vaccine prevented nearly 60% of medically attended influenza visits across 2 influenza seasons for individual and combined age groups of children. An estimated 5% to 10% of children have an influenza-related ARI visit each year and the visit often results in an antibiotic prescription [1,2,27]. This study and others' suggest that widespread influenza vaccination of children will have a major impact on health care utilization. Our study supports recommendations from the CDC to vaccinate young children against influenza disease and highlights the importance of full vaccination, since partial vaccination showed no significant VE" • Well-reported and well conducted study, the only concern is about real effect of the matching procedure adopted by the authors. We are uncertain as to whether it assures good comparability between cases and control

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
CC-Case Selection	Low risk	Independent validation
CC-Control Selection	Low risk	Drawn from the same population
CC-Comparability	Unclear risk	Matched
CC-Exposure	Low risk	Secure record and interview
Summary assessments	Unclear risk	Plausible bias that raises some doubt about the results

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ba Valenciano 2011

Methods	A multicentre case-control study based on sentinel practitioner surveillance networks from seven European countries was undertaken to estimate the effectiveness of 2009-2010 pandemic and seasonal influenza vaccines against medically attended ILI laboratory-confirmed as pandemic influenza A (H1N1) (pH1N1) The study was conducted within the context of the existing European Influenza Surveillance Network (EISN) [12]. At the seven study sites, EISN sentinel primary care practitioners were invited to participate in the study. In Portugal and Italy, practitioners other than those participating in EISN, were also invited to participate The study population consisted of patients consulting a participating practitioner for ILI (six sites) or ARI (France) and having a nasal or throat swab taken within an interval of less than 8 days after symptom onset In Hungary, the study population was restricted to patients aged more than 17 years. In Italy, the study population was restricted to patients who belonged to the groups for which the pandemic vaccine was recommended In five of the seven study sites practitioners used a systematic random sample to select the patients to swab. In Ireland each participating practice was asked to take a nasal or throat swab from five patients presenting with ILI each week In France, each practitioner had an age group assigned and swabbed the first ARI patient of the week in the allocated age group Exclusion criteria Individuals who tested positive for influenza A but had a non-typeable strain, those testing positive for other strains of influenza A or for influenza B and those with missing information on laboratory results, were excluded
Participants	Description of cases A case of pandemic influenza A (H1N1) 2009 (pH1N1 case) was an ILI patient (defined according to the EU case definition as sudden onset of symptoms and at least 1 of the following four systemic symptoms: fever or feverishness, malaise, headache, myalgia and at least 1 of the following three respiratory symptoms: cough, sore throat, shortness of breath) who was swabbed and tested positive for the pH1N1 using real-time (RT) PCR or culture Swabs were tested for influenza at the respective countries' National Influenza Reference Laboratory. In France, Italy and Spain, tests were also conducted in other laboratories participating in the National Influenza Sentinel Surveillance System Description of controls Controls were ILI patients who were swabbed and tested negative for any influenza virus
Interventions	Exposure (Interventions) For pandemic and seasonal influenza vaccine, individuals were considered vaccinated if they had received a dose of the vaccine more than 14 days before the date of onset of ILI symptoms and UV if they had received no vaccine or the vaccine was given less than 15 days before the onset of ILI symptoms Vaccination status was ascertained using the practitioners' medical records or during the patient interview Each of the seven study teams entered and validated data. Validation of the vaccination status and of other

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ba Valenciano 2011 (*Continued*)

	variables was attempted by contacting the practitioner or by checking existing vaccination registries in the case of missing information
Outcomes	pH1N1 using real-time (RT) PCR or culture
Funding Source	Government
Notes	The authors conclude that results suggest good protection of the pandemic monovalent vaccine against medically attended pH1N1 and no effect of the 2009-2010 seasonal influenza vaccine. However, the late availability of the pandemic vaccine and subsequent limited coverage with this vaccine hampered our ability to study vaccine benefits during the outbreak period. Future studies should include estimation of the effectiveness of the new trivalent vaccine in the upcoming 2010-2011 season, when vaccination will occur before the influenza season starts

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
CC-Case Selection	Low risk	Independent validation
CC-Control Selection	Low risk	Drawn from the same population
CC-Comparability	Low risk	Adjustment by confounders
CC-Exposure	Low risk	Interview
Summary assessments	Low risk	Possible under-estimation of vaccine efficacy

ba Van Buynder 2010

Methods	Pandemic vaccines; case-control study on vaccine efficacy Carried out on children under 10 years with ILI who were tested for H1N1 infection at the central provincial laboratory Laboratory-confirmed influenza was the primary outcome and vaccination status the primary exposure to assess VE
Participants	All children throughout New Brunswick, 6 months to 9 years of age, who were tested for H1N1 were selected for inclusion Description of cases Children were classified as cases if the respiratory sample was H1N1 positive Description of controls They were classified as a control if the test was negative and the child met a clinical case definition of ILI (the presence of fever and at least 1 respiratory symptom or sign). Information on age, sex, hospitalisation, indigenous status, prematurity, immunosuppression, coexisting medical conditions, previous seasonal vaccination and recent pandemic vaccination was collected by direct telephone interview The diagnosis of an ILI was confirmed using a simple questionnaire. The interviews were conducted by staff from CDCB

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ba Van Buynder 2010 (*Continued*)

Interventions	Vaccination status and date of vaccination was determined through access to New Brunswick's universal pandemic vaccination registration programme. This programme recorded the personal details of every person vaccinated in New Brunswick including the date of administration. Children were classified as vaccinated if the child had received a dose of the H1N1 vaccine at least 14 days before the onset of symptoms and as 'not vaccinated' if the child received no vaccination or received the first dose < 14 days before the onset of symptoms. No child in the study was 14 days post-receipt of a second dose of vaccine
Outcomes	
Funding Source	Government
Notes	The authors conclude that: "A single 0.25 ml dose of the GSK adjuvanted vaccine (Arepanrix^{TM}) protects children against laboratory-confirmed pandemic influenza potentially avoiding any increased reactogenicity associated with second doses. Adjuvanted vaccines offer hope for improved seasonal vaccines in the future" This is a poorly reported study in which selection criteria for cases are not clearly described

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
CC-Case Selection	High risk	Not sufficient description
CC-Control Selection	Unclear risk	Possibly drawn from the same population
CC-Comparability	Unclear risk	Adjustment by confounding factors
CC-Exposure	Unclear risk	Structured interview
Summary assessments	High risk	Plausible bias that seriously weakens confidence in the results

ca Yin 2011

Methods	Prospective cohort study carried out on children aged 6 to 59 months from 2 daycare centres (DCC) and 2 preschool centres (PSC) Effectiveness of trivalent inactivated seasonal vaccine in preventing ILI cases was assessed
Participants	Children from 2 care centres (DCC1, n = 62 and DCC2, n = 73; age range 6 to 59 months) and 2 preschool centres (PSC1, n = 52 and PSC2, n = 52; age range 24 to 59 months) in Sydney
Interventions	Administered vaccine was VAXIGRIP JUNIOR (Sanofi Pasteur, Lyon, France) prepared with the strain recommended for the 2007 in the Southern Hemisphere: • A/New Caledonia/20/99 (H1N1)-like strain (A/New Caledonia/20/99 IVR-116) • A/Wisconsin/67/2005 (H3N2)-like strain (A/Wisconsin/67/2005 NYMCX-161B) • B/Malaysia/2506/2004-like strain • Children were immunised with 2 doses of 0.5 ml (0.25 ml if aged less than 36

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	months) 1 month apart intramuscularly administered • Children from DCC1 and PSC1 were immunised, whereas those from DCC2 and PSC2 acted as control group and did not receive any treatment Immunisation has been performed between 11 July 2007 and 19 September 2007
Outcomes	Laboratory Parents were trained from study nurses in order to collect nasal swabs by means of the Virocult system. Samples were sent by post to the Queensland Paediatric Infectious Diseases Laboratory, where the presence of the following viruses has been investigated: human rhinoviruses (HRV), influenza A, influenza B, RSV, adenoviruses, HMPV, parainfluenza viruses I, II and III, bocavirus, hPyV-WU, hPyV-KI and human coronaviruses OC43, 229E, NL6332 and HKU1.33 Effectiveness ILI: defined as illness with fever > 37.8°C and at least 1 respiratory symptom (cough, blocked nose or runny nose). Cases were assessed by parents after education for ILI surveillance. This was begun 2 weeks after the 2nd dose among vaccinated and from August 26th, 2007 onwards among controls and was continued up to October 21st, 2007. Households were also invited to monitor ILI symptoms by mail or phone call between July 30th and October 21st, 2007 Safety Not assessed
Funding Source	Government
Notes	• Allocation of DCC and PSC to vaccination or no treatment did not occur randomly (see discussion), even if this was stated in the methods • Only 151 out of the total 239 children (63%) from DCC 1 and 2 and PSC 1 and 2 were enrolled in the study • 1 vaccinated child from PSC1 was further lost from follow-up • Nasal swab samples had been collected for only 26 out of 59 detected ILI cases. In 18 samples the presence of at least 1 virus could be assessed, only 2 tested positive for influenza A viruses • At the time when follow-up was started (mid-August), the epidemic was peaking The authors conclude that "No evidence was found for influenza VE but point estimates were all in the direction of protection"

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
PCS/RCS-Selection Exposed cohort	Unclear risk	Not clearly described
PCS/RCS-Selection Non Exposed cohort	Unclear risk	Not clearly described
PCS/RCS-Comparability	Unclear risk	Not clearly described
PCS/RCS-Assessment of Oucome	Unclear risk	Self-report

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ca Yin 2011 (*Continued*)

Summary assessments	High risk	Plausible bias that seriously weakens confidence in the results

cb MPA 2011

Methods	Person-time cohort study, based on a case inventory of narcolepsy cases observed in the 6 Swedish countries between 2009 and 2010 in order to assess its possible association with exposure to pandemic flu monovalent vaccine (PANDREMIX) in children and adolescents, conducted by Medical Product Agency (MPA)
Participants	Cases of narcolepsy with cataplexy were identified from: • departments of neurology, paediatrics, paediatric neurology, or paediatric psychiatry of hospitals, sleep laboratories and laboratories of clinical physiology, which perform multiple sleep latency tests (MSLT), MPA database on spontaneous ADR reports on narcolepsy Medical records were collected for cases which had been diagnosed or were under review during 2009 through 2010 2 external clinical experts in neurology/sleep disorders were commissioned by the MPA to review the medical records of all the collected cases and to classify (independently of each other) the diagnosis according to the American Academy of Sleep Medicine criteria for narcolepsy with catalepsy (see Safety) and to assess the onset of the narcolepsy disease through dating of the first symptom of narcolepsy. For the case of discrepancy a third review was performed by an external expert in paediatric neurology. In the preliminary study only cases occurred in Stockholm, Västra Götaland, Östergötland and Skåne countries in participants aged below 19 were considered, whereas the whole Swedish "under 19" age class was included in the whole study
Interventions	• Immunisation with pandemic H1N1 vaccine "Pandremix" in the vaccination campaign that took place in Sweden between mid-October 2009 and March 2010 Incident exposed cases occurred during the pandemic period (after October 1st, 2009) were defined vaccinated if they had the date of vaccination before the date of first symptom of narcolepsy (at least 1 vaccine dose). Cases were classified as non-exposed when there was no exposure to vaccination or when vaccination had occurred after onset of symptoms or during the same month as onset of symptoms
Outcomes	Laboratory Not assessed Effectiveness Not assessed Safety Incidence of narcolepsy with catalepsy was compared between vaccinated and not vaccinated participants. Diagnosis in medical records was reviewed by 2 neurologists accordingly to the American Academy of Sleep Medicine diagnostic criteria for narcolepsy with catalepsy: • Excessive daytime sleepiness occurring almost daily for at least 3 months • Definite history of cataplexy, defined as sudden and transient (less than 2 minutes) episodes of loss of muscle tone, generally bilateral, triggered by emotions (usually laughing and joking)

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	• Diagnosis should, whenever possible, be confirmed by nocturnal polysomnography (with a minimum of 6 hours sleep) followed by a daytime MSLT: ○ Mean daytime sleep latency 8 minutes or shorter, with 2 or more sleep onset in REM periods (the time from sleep onset to REM sleep should be less than 15 minutes in at least 2 naps) ○ Alternatively, hypocretin-1 concentrations in the cerebrospinal fluid 110 pg/ml or lower, or a third of mean control values • The hypersomnia is not better explained by another sleep disorder, medical or neurological disorder, mental disorder, medication use, or substance use disorder Altogether 87 cases of narcolepsy with catalepsy were confirmed after review of the 135 cases initially identified. Out of them, 69 were vaccinated before onset of the first symptom, 7 were not vaccinated or had symptoms onset before vaccination, a further 6 were also not vaccinated and thus had onset of first symptoms before January 1st, 2009 and were therefore excluded from the study. A further 5 cases were classified under "unknown vaccination status" because they had vaccination during the same month of onset
Funding Source	Government
Notes	In the preliminary registry-based study, carried out on the population of four counties (Stockholm, Västra Götaland, Östergötland and Skåne) within which vaccination register and health care data were accessible and available, all participants registered in the respective county on October 1st 2009 without a known diagnosis of narcolepsy were followed until December 31st 2010, date of narcolepsy diagnosis, death or migration from the county, whichever came first. In the cohort of vaccinated participants the follow-up time was defined as exposure from the date of vaccination until the end of follow-up. Vaccinated participants contributed with exposure time in the UV cohort from October 1st to the date of vaccination. The incidence rates in the vaccinated and UV cohorts, respectively, were calculated as the number of persons diagnosed with an incident registration for narcolepsy in the health data bases, divided by the person years at risk. The relative risk, vaccinated versus UV cohorts, was calculated as the corresponding ratio of incidence rates. Exact CIs for relative risk were calculated through exact CIs for binomial proportions. Since there is no nationwide vaccination register, it was not possible to calculate the risk time directly for the total vaccinated and non-vaccinated cohorts in all of Sweden. However, risk time was extrapolated from the registry based study, using data from four counties/regions of Sweden. It is not clear how the 5 cases with symptom onset and vaccination within the same month has been considered. They has been initially classified as not vaccinated (see page 5, lines 4 to 5 from the top, i.e. 9 vaccinated cases vs 7+5 not vaccinated cases), has been simply excluded from the main analysis (69 vaccinated cases vs 7 not vaccinated cases), then authors considers, erroneously, these 5 as part of the 7 unexposed in the "sensitivity analysis" (see page 6, 3rd paragraph from the top and page 7, 4th paragraph from the bottom). It would be useful to complete the sensitivity analysis considering the 5 with uncertain vaccine exposure among vaccinated first and among not vaccinated. The authors conclude that "These new results provide strengthened evidence that vaccination with Pandemrix during the pandemic period was associated with an increase in the risk for narcolepsy with cataplexy in children/adolescents 19 years and younger.

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cb MPA 2011 (*Continued*)

	Further research is urgently needed to explain the possible causative mechanisms"

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
PCS/RCS-Selection Exposed cohort	Low risk	Secure record
PCS/RCS-Selection Non Exposed cohort	Low risk	Secure record
PCS/RCS-Comparability	Unclear risk	Retrospective study
PCS/RCS-Assessment of Oucome	Low risk	Secure record
Summary assessments	Low risk	

aa Bracco Neto 2009b

Methods	See Bracco Neto 2009a (Year 2 = 2002)
Participants	See Bracco Neto 2009a
Interventions	See Bracco Neto 2000a
Outcomes	See Bracco Neto 2009a
Funding Source	See Bracco Neto 2009a
Notes	

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Second year of the same randomisation procedure
Allocation concealment (selection bias)	Unclear risk	No descriptions, second year of the same study design
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No descriptions, second year of the same study design
Incomplete outcome data (attrition bias) All outcomes	High risk	Year of the same study design

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aa Bracco Neto 2009b (*Continued*)

Summary assessments	High risk	Plausible bias that raises some doubt about the results

ba Eisenberg 2008b

Methods	See Eisenberg 2008a
Participants	
Interventions	
Outcomes	
Funding Source	
Notes	

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
CC-Case Selection	Low risk	Independent validation
CC-Control Selection	Low risk	Same population
CC-Comparability	Low risk	Adjustment by confounders
CC-Exposure	Low risk	Secure record
Summary assessments	Low risk	Plausible bias unlikely to seriously alter the results

aa Tam 2007b

Methods	see Tam 2007a (year 2)
Participants	
Interventions	
Outcomes	
Funding Source	
Notes	

Risk of bias ***Risk of bias***

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aa Tam 2007b (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number
Allocation concealment (selection bias)	Low risk	"At enrolment, each subject was assigned the next sequential subject number and received study product of the treatment code assigned to that subject number according to a preprinted randomisation allocation list"
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Possibility of biased follow-up and reporting bias
Summary assessments	Low risk	Plausible bias unlikely to seriously alter the results

ba Cochran 2010b

Methods	see ba Cochran 2010a
Participants	
Interventions	
Outcomes	
Funding Source	
Notes	

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
CC-Case Selection	High risk	Not clearly described
CC-Control Selection	Unclear risk	Apparently same population
CC-Comparability	High risk	Insufficient description
CC-Exposure	Unclear risk	Secure record
Summary assessments	High risk	Lack of information about study design and matching method

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ba Cochran 2010c

Methods	see ba Cochran 2010a
Participants	
Interventions	
Outcomes	
Funding Source	
Notes	

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
CC-Case Selection	High risk	
CC-Control Selection	Unclear risk	Apparently same population
CC-Comparability	High risk	Insufficient description
CC-Exposure	Unclear risk	Secure record
Summary assessments	High risk	Lack of information about study design and matching method

ba Staat 2011b

Methods	See Staat 2011b
Participants	
Interventions	
Outcomes	
Funding Source	
Notes	

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
CC-Case Selection	Low risk	Independent validation
CC-Control Selection	Low risk	Drawn from the same population

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ba Staat 2011b (*Continued*)

CC-Comparability	Unclear risk	Matched
CC-Exposure	Low risk	Secure record and interview
Summary assessments	Unclear risk	Plausible bias that raises some doubt about the results

ACIP: Advisory Committee on Immunization Practices
AOM: acute otitis media
ARI: acute respiratory infection
CAIV-T: cold-adapted influenza vaccine, trivalent
CCA: chick cell-agglutinating
CCT: comparative controlled trial
CI: confidence interval
C-RCT: cluster-randomised controlled trial
ICD: international code disease
ILI: influenza-like illness
FV: fully vaccinated
HA: haemagglutinin
HAI: haemagglutination antibody inhibition
HMO: Health Maintainance Organisation
HPMG: HealthPartners Medical Group
HR: hazard ratio
LAIV: live attenuated influenza vaccine
N/A: not applicable
OM: otitis media
OME: otitis media with effusion
OR: odds ratio
PAE: adverse event
PCR: polymerase chain reaction
P&I: pneumonia & influenza
PV: partially vaccinated
qRT-PCR: real time polymerase chain reaction
RCT: randomised controlled trial
RSV: respiratory syncytial virus
RCT-PCR: reverse transcription polymerase chain reaction
SAE: serious adverse event
TIV: trivalent influenza vaccine
TM: tympanic membrane
URTI: upper respiratory tract infection
UV: unvaccinated
VE: vaccine efficacy/effectiveness
VSD: vaccine safety data link
WHO: World Health Organization

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

Study	Reason for exclusion
Ambrose 2011	Pooled analysis of safety data from 20 RCTs of LAIV
Anderson 1992	Only serological outcomes presented
Anonymous 2003	Editorial only
Beare 1968	Study subjects were adults
Belshe 2000b	Only serological outcomes presented
Belshe 2000c	Only aggregated outcomes presented, duplicate publication of Belshe 1998 and 2000
Belshe 2008	Data from studies already included in previous studies
Bergen 2004	Outcomes only presented if statistically significantly increased or decreased risk in vaccinated group. Outcomes were presented by age group and setting. Authors declined to grant access to data from settings and age groups where outcomes were not significantly different between treatment and control
Betts 1977	Study subjects were university students aged 18 to 25
Beutner 1976	Same study as Beutner 1979 (included)
Bichurina 1982	No denominators presented
Boyce 1999	No clinical outcomes for efficacy and safety
Boyce 2000	Study population aged 18 to 40
Boyer 1977	Only serological outcomes were presented
Chow 1979	Serological study on part of study population of Beutner 1979
Clements 1995	Hepatitis B vaccine as control
Coles 1992	Study population consisted of elderly and staff from nursing home
Daubeney 1997	High risk children
Donatelli 1998	No control (split vaccine versus trivalent subunit-type)
Eddy 1970	Subjects were healthy adult males
Edwards 1994	Placebo arm present only in the first study year, for which neither efficacy nor safety data are available Age group is 1 to 65 years and no data is presented for children only

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(*Continued*)

El'shina 1998	Age group 18 to 23
Feldman 1985	Only serological outcomes presented
Foy 1981	No control
France 2004	Case cross-over
Fujieda 2008	Same data of Fujieda 2006 already included
Gaglani 2004	Ecological study
Gendon 2004	Study addresses the question of whether vaccinating children interrupts transmission to elderly. Study should be included in the elderly review
Glezen 2001	Comment only (on Hurwitz 2000a)
Groothuis 1994	Study subjects were children with chronic pulmonary diseases; no control
Groothuis 1998	Trial of respiratory syncytial virus (RSV) vaccine
Gross 1977a	Only serological outcomes
Gross 1977b	No placebo control
Gross 1982	All recipients had cystic fibrosis
Gruber 1993	Follow-up times for safety outcomes variable within groups. Total follow-up time not stated in methods, refers to other papers for methodology
Haba-Rubio 2011	Case report of cases of narcolepsy
Halperin 2002	Study subjects had chronic cardiac or pulmonary disorders
Hambidge 2006	Case cross-over study
Hatch 1956	No control
Heikkinen 2003	Survey carried out on children younger than 13 years to determine the attack of flu virus in those having fever or respiratory infections
Hoskins 1973	No placebo control - excluded because an influenza B vaccine was used as control
Hoskins 1979	No control
Howell 1964a	Adult population

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(*Continued*)

Howell 1964b	Adult population
Hrabar 1977	Probably more than 25% of the study subjects are older than 25 years (mean 15.8; range 14.0 to 17.9); efficacy outcomes only serological
Hurwitz 2000a	Hepatitis A vaccine as control
Hurwitz 2000b	Hepatitis A vaccine as control
Jansen 2008	Head to head: TIV+PCV7 vs TIV+PLA vs HBV+PLA
Jovanovic 1979	Non-experimental design
Jurgenssen 1978	No placebo control
Just 1978	No placebo control
Karron 1995	Influenza vaccine administered with routine immunisation
Kaufman 2000	Telephone survey to estimate the compliance rate with influenza vaccination
King 2001	Study included HIV-infected groups and uninfected groups, uninfected groups excluded because trial was a cross-over design, safety data for 1st, 2nd and 3rd doses was pooled so could not be used (some placebo recipients would have received vaccine 4 to 5 weeks previously and participants would be included in N for placebo and vaccine)
Kissling 2011a	Data already presented in Kissling 2011
Kramarz 2001	Study subjects are children with asthma
Kuno-Sakai 1994	Study subjects are aged 16 to 17 years. No control
La Montagne 1983	No original data presented
Lauteria 1974	Study population aged 18 to 24
Lerman 1977	Only serological data presented
Lina 2000	No control
Longini 2000	Comment on Belshe 1998 and 2000 only
Luce 2001	Cost-effectiveness analysis based on the results of Belshe 1998 and 2000
Luthardt 1979	No placebo control
Marchisio 2002	Study subjects are children with recurrent otitis media

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(*Continued*)

Martin Moreno 1998	Review
Maynard 1968	No placebo control
McMahon 2008	Non-comparative study
Mendelman 2001	Review
Monto 1970	Subjects vaccinated just before or during epidemic. Vaccine effectiveness expressed as O-E. No numerator or denominator data reported
Monto 1977	Review
Morio 1994	Only cumulative data from three years were reported to evaluate the effectiveness
Morris 1976	Study subjects are college students aged 18 to 29
Muhammad 2011	Non-comparative study
Neuzil 2001	Re-analysis of Edwards 1994 (in which placebo arm was present only in the first study year, neither efficacy or safety data are available)
Neuzil 2006	Non-comparative study
Nolan 2003	No control (two different commercial preparations of the same vaccine were compared)
Ogra 1977	Same study as Beutner 1979
Piedra 1991	Three studies in one. Two already included, the third is of uncertain provenance
Piedra 1993	Safety data are given cumulatively on 3-year study
Piedra 2002b	All the data in this paper is presented in either Piedra 2002 or King 1998; both included
Quach 2003	Analysis of factors associated with hospitalisation
Rimmelzwaan 2000	Subjects aged 18 to 55 years
Ruben 1973	No placebo control
Schaad 2000	Study population consists of children and adolescents with cystic fibrosis
Scheifele 1990	Non-comparative studies
Schiff 1975	Safety outcomes combined for first and second doses of vaccine
Slepushkin 1993	Subjects received vaccine or placebo depending on their age

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(*Continued*)

Stowe 2011	Case series or case cross-over
Sugaya 1994	Study subjects are children with moderate to severe asthma
Sumaya 1977	Only serological data are presented
Van Hoecke 1996	No control
Vasil'eva 1986	No denominators presented
Vasil'eva 1987	Denominators for vaccinated and placebo groups were combined in results tables
Wahlberg 2003	Trial of HiB vaccine
Welty 1977a	Safety outcomes only with no placebo control
Welty 1977b	Safety outcomes only with no placebo control
Wesselius-de 1972	Only serological efficacy outcomes presented
Wright 1976b	Data duplicated in Wright 1976a
Wright 1985	Only immune responses and viral shedding outcomes presented
Wu 2010	Efficacy cohort with inadequate follow-up length
Zhilova 1986	Study population aged 18 to 23

HBV: hepatitis B vaccine
HBV+PLA: human B virus + placebo
HiB: Haemophilus influenzae b
LAIV: live attenuated influenza vaccine
O-E: observed-expected
PCV: pneumococcal conjugate vaccine
PLA: placebo
RCT: randomised controlled trial
TIV: trivalent influenza vaccine
TIV+PCV7: trivalent influenza vaccine + pneumococcal vaccine, eptaValent
TIV+PLA: trivalent influenza vaccine + placebo

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DATA AND ANALYSES

Comparison 1. Live vaccine versus placebo or no intervention (RCTs by age group)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Influenza	6	9175	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.13, 0.32]
1.1 under 2 years	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 under 6 years	6	9115	Risk Ratio (M-H, Random, 95% CI)	0.18 [0.11, 0.29]
1.3 over 6 years	1	60	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.23, 0.97]
2 Influenza-like illness	8	188418	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.62, 0.72]
2.1 under 2 years	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 under 6 years	5	38646	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.57, 0.77]
2.3 over 6 years	8	149772	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.60, 0.74]

Comparison 2. Inactivated vaccine versus placebo or no intervention (RCTs by age group)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Influenza	5	1628	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.29, 0.59]
1.1 under 2 years	2	786	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.18, 1.69]
1.2 under 6 years	2	132	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.34, 1.08]
1.3 over 6 years	3	710	Risk Ratio (M-H, Random, 95% CI)	0.31 [0.22, 0.45]
2 Influenza-like illness	5	19388	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.54, 0.76]
2.1 under 2 years	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 under 6 years	3	476	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.21, 0.69]
2.3 over 6 years	4	18912	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.66, 0.78]

Comparison 3. Live attenuated vaccines (cohort studies by age group)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Influenza	1	83	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.35, 0.91]
1.1 under 2 years	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 under 6 years	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 over 6 years	1	83	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.35, 0.91]
2 Influenza-like illness	2	22077	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.57, 0.69]
2.1 under 2 years	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 under 6 years	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 over 6 years	2	22077	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.57, 0.69]

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Comparison 4. Inactivated vaccines (cohort studies by age group)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Influenza	6	1873	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.25, 0.73]
1.1 under 2 years	3	314	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.27, 1.47]
1.2 under 6 years	1	180	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.13, 0.89]
1.3 over 6 years	2	1379	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.12, 1.11]
2 Influenza-like illness	11	11935	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.42, 0.67]
2.1 under 2 years	1	23	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.23, 0.93]
2.2 under 6 years	5	7046	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.59, 0.93]
2.3 over 6 years	7	4866	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.29, 0.68]
3 Otitis media	1	119	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.22, 1.03]
3.1 Children aged 6 months to 5 years	1	119	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.22, 1.03]

Comparison 5. Live vaccine versus placebo (RCTs)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Influenza	6	6081	Risk Ratio (M-H, Random, 95% CI)	0.19 [0.11, 0.32]
1.1 Live attenuated vaccines (one-dose)	5	3038	Risk Ratio (M-H, Random, 95% CI)	0.23 [0.12, 0.47]
1.2 Live attenuated vaccines (two-doses)	2	3043	Risk Ratio (M-H, Random, 95% CI)	0.11 [0.04, 0.26]
2 Influenza-like illness	7	124606	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.60, 0.80]
2.1 Live attenuated vaccines (one-dose)	2	3306	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.18, 2.22]
2.2 Live attenuated vaccines (two-doses)	6	121300	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.57, 0.76]
3 Otitis media (all episodes)	2	2873	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.95, 1.01]
4 Working days lost (number of events, parents)	2	2874	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.46, 1.03]
5 Drug prescriptions (number of events)	1	1784	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.87, 1.12]
6 Outpatients attendance for pneumonia and influenza	2	2874	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.59, 0.98]

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Comparison 6. Inactivated vaccine versus placebo (RCTs)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Influenza	5	1628	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.28, 0.48]
1.1 Inactivated vaccines (one-dose)	5	1628	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.28, 0.48]
1.2 Inactivated vaccines (two-doses)	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Influenza-like illness	4	19044	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.65, 0.79]
2.1 Inactivated vaccines (one-dose)	2	267	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.15, 0.81]
2.2 Inactivated vaccines (two-doses)	2	18777	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.69, 0.76]

Comparison 7. Case-control studies

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Influenza vs influenza-like illness (crude data)	9		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Children aged below 6	9	4949	Odds Ratio (M-H, Random, 95% CI)	0.59 [0.45, 0.77]
1.2 Children aged between 5-19	1	27	Odds Ratio (M-H, Random, 95% CI)	0.76 [0.07, 8.66]
2 Influenza vs influenza-like illness (adj. estimates)	9		Odds Ratio (Random, 95% CI)	Subtotals only
2.1 Children aged below 23 months - fully vaccinated	7		Odds Ratio (Random, 95% CI)	0.60 [0.39, 0.94]
2.2 Children aged between 24-59 months - fully vaccinated	4		Odds Ratio (Random, 95% CI)	0.40 [0.22, 0.70]
2.3 Children aged between 6 - 59 months - fully vaccinated	5		Odds Ratio (Random, 95% CI)	0.45 [0.32, 0.62]
2.4 Children aged below 14 years old - fully vaccinated	1		Odds Ratio (Random, 95% CI)	0.23 [0.06, 0.84]
3 Influenza-like illness vs no symptoms	1	488	Odds Ratio (M-H, Random, 95% CI)	0.49 [0.28, 0.86]
3.1 Inactivated vaccine (one-dose)	1	244	Odds Ratio (M-H, Random, 95% CI)	0.53 [0.26, 1.07]
3.2 Inactivated vaccine (two-doses)	1	244	Odds Ratio (M-H, Random, 95% CI)	0.44 [0.18, 1.10]

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Comparison 8. Vaccine versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Influenza	8	6590	Risk Ratio (M-H, Random, 95% CI)	0.27 [0.18, 0.42]
1.1 Live attenuated vaccines (one-dose)	4	1919	Risk Ratio (M-H, Random, 95% CI)	0.27 [0.12, 0.61]
1.2 Live attenuated vaccines (two-doses)	2	3043	Risk Ratio (M-H, Random, 95% CI)	0.11 [0.04, 0.26]
1.3 Inactivated vaccines (one-dose)	5	1628	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.28, 0.48]
1.4 Inactivated vaccines (two-doses)	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Influenza-like illness	8	143650	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.62, 0.77]
2.1 Live attenuated vaccines (one-dose)	2	3306	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.18, 2.22]
2.2 Live attenuated vaccines (two-doses)	6	121300	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.57, 0.76]
2.3 Inactivated vaccines (one-dose)	2	267	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.15, 0.81]
2.4 Inactivated vaccines (two-doses)	2	18777	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.69, 0.76]
3 Secondary cases	1	123	Risk Ratio (M-H, Random, 95% CI)	1.68 [0.56, 4.99]
3.1 Live attenuated vaccines (one-dose)	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 Live attenuated vaccines (two-doses)	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.3 Inactivated vaccines (one-dose)	1	123	Risk Ratio (M-H, Random, 95% CI)	1.68 [0.56, 4.99]
3.4 Inactivated vaccines (two-doses)	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4 School absenteeism	1	550	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.26, 0.92]
4.1 Live attenuated vaccines (one-dose)	1	296	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.22, 1.19]
4.2 Live attenuated vaccines (two-doses)	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.3 Inactivated vaccines (one-dose)	1	254	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.17, 1.22]
4.4 Inactivated vaccines (two-doses)	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5 Lower respiratory tract disease	2	1632	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.03, 1.54]
5.1 Live attenuated vaccines (one-dose)	2	1496	Risk Ratio (M-H, Random, 95% CI)	0.16 [0.01, 4.45]
5.2 Live attenuated vaccines (two doses)	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5.3 Inactivated vaccines (one-dose)	1	136	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.01, 6.17]
5.4 Inactivated vaccines (two-doses)	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

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6 Acute otitis media	6	5253	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.79, 1.26]
6.1 Live attenuated vaccines (one-dose)	3	2585	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.05, 3.79]
6.2 Live attenuated vaccines (two-doses)	1	1784	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.95, 1.01]
6.3 Inactivated vaccines (one-dose)	1	136	Risk Ratio (M-H, Random, 95% CI)	1.52 [0.10, 23.76]
6.4 Inactivated vaccines (two-doses)	2	748	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.95, 1.40]
7 Hospitalisation due to acute otitis media	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 Inactivated vaccine (two-doses)	2	765	Risk Ratio (M-H, Random, 95% CI)	1.41 [0.62, 3.24]
8 Consequences of acute otitis media	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
8.1 Inactivated vaccine (two-doses - visits)	2	765	Mean Difference (IV, Random, 95% CI)	-0.02 [-0.27, 0.23]
8.2 Inactivated vaccine (two-doses - courses of antibiotics)	2	765	Mean Difference (IV, Random, 95% CI)	0.13 [-0.36, 0.63]
9 Outpatients attendance for pneumonia and influenza	2	2874	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.59, 0.98]
9.1 Live attenuated vaccine (one-dose)	1	1090	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.49, 0.85]
9.2 Live attenuated vaccine (two-doses)	1	1784	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.75, 0.96]
10 Working days lost (number of events, parents of children 6-36 months of age)	2	2874	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.46, 1.03]
10.1 Live attenuated vaccine	2	2874	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.46, 1.03]
11 Drug prescriptions (number of events, 6-36 months of age)	1	1784	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.87, 1.12]
11.1 Live attenuated vaccine	1	1784	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.87, 1.12]

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Analysis 1.1. Comparison 1 Live vaccine versus placebo or no intervention (RCTs by age group), Outcome 1 Influenza.

Review: Vaccines for preventing influenza in healthy children

Comparison: 1 Live vaccine versus placebo or no intervention (RCTs by age group)

Outcome: 1 Influenza

Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 under 2 years					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Vaccine), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 under 6 years					
aa Belshe 1998	14/1070	95/532		14.2 %	0.07 [0.04, 0.13]
aa Tam 2007a	98/1900	204/1274		17.0 %	0.32 [0.26, 0.41]
aa Vesikari 2006a	23/1059	97/725		15.3 %	0.16 [0.10, 0.25]
aa Clover 1991	5/27	20/51		11.1 %	0.47 [0.20, 1.12]
aa Vesikari 2006b	31/658	148/461		16.0 %	0.15 [0.10, 0.21]
aa Belshe 2000a	15/917	51/441		14.1 %	0.14 [0.08, 0.25]
Subtotal (95% CI)	**5631**	**3484**		**87.6 %**	**0.18 [0.11, 0.29]**
Total events: 186 (Vaccine), 615 (Control)					
Heterogeneity: $Tau^2 = 0.31$; $Chi^2 = 38.05$, df = 5 (P<0.00001); I^2 =87%					
Test for overall effect: Z = 6.81 (P < 0.00001)					
3 over 6 years					
aa Clover 1991	7/29	16/31		12.4 %	0.47 [0.23, 0.97]
Subtotal (95% CI)	**29**	**31**		**12.4 %**	**0.47 [0.23, 0.97]**
Total events: 7 (Vaccine), 16 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.04 (P = 0.041)					
Total (95% CI)	**5660**	**3515**		**100.0 %**	**0.20 [0.13, 0.32]**
Total events: 193 (Vaccine), 631 (Control)					
Heterogeneity: $Tau^2 = 0.32$; $Chi^2 = 42.54$, df = 6 (P<0.00001); I^2 =86%					
Test for overall effect: Z = 6.72 (P < 0.00001)					
Test for subgroup differences: $Chi^2 = 4.55$, df = 1 (P = 0.03), I^2 =78%					

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Analysis 1.2. Comparison 1 Live vaccine versus placebo or no intervention (RCTs by age group), Outcome 2 Influenza-like illness.

Review: Vaccines for preventing influenza in healthy children

Comparison: 1 Live vaccine versus placebo or no intervention (RCTs by age group)

Outcome: 2 Influenza-like illness

Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 under 2 years					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Vaccine), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 under 6 years					
aa Alexandrova 1986	447/3538	853/3271		9.1 %	0.48 [0.44, 0.54]
aa Clover 1991	2/27	7/51		0.3 %	0.54 [0.12, 2.42]
aa Rudenko 1996b	1696/6982	2303/6721		10.3 %	0.71 [0.67, 0.75]
aa Rudenko 1996a	2540/8117	3564/7524		10.5 %	0.66 [0.63, 0.69]
aa Rudenko 1988	285/1224	310/1191		8.0 %	0.89 [0.78, 1.03]
Subtotal (95% CI)	**19888**	**18758**		**38.2 %**	**0.67 [0.57, 0.77]**
Total events: 4970 (Vaccine), 7037 (Control)					
Heterogeneity: Tau^2 = 0.02; Chi^2 = 58.65, df = 4 (P<0.00001); I^2 =93%					
Test for overall effect: Z = 5.28 (P < 0.00001)					
3 over 6 years					
aa Alexandrova 1986	516/13092	902/11240		9.0 %	0.49 [0.44, 0.55]
aa Grigor'eva 2002	64/539	51/297		3.5 %	0.69 [0.49, 0.97]
aa Clover 1991	0/29	4/31		0.1 %	0.12 [0.01, 2.11]
aa Rudenko 1993a	711/4693	1062/4198		9.6 %	0.60 [0.55, 0.65]
aa Rudenko 1996b	4024/25113	6214/28164		10.6 %	0.73 [0.70, 0.75]
aa Rudenko 1996a	4069/21573	7296/24345		10.6 %	0.63 [0.61, 0.65]
aa Rudenko 1993b	1093/4870	2033/6201		10.1 %	0.68 [0.64, 0.73]
aa Rudenko 1988	351/2599	385/2788		8.2 %	0.98 [0.85, 1.12]
Subtotal (95% CI)	**72508**	**77264**		**61.8 %**	**0.67 [0.60, 0.74]**
Total events: 10828 (Vaccine), 17947 (Control)					
Heterogeneity: Tau^2 = 0.02; Chi^2 = 104.96, df = 7 (P<0.00001); I^2 =93%					
Test for overall effect: Z = 7.59 (P < 0.00001)					
Total (95% CI)	**92396**	**96022**		**100.0 %**	**0.67 [0.62, 0.72]**

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Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Total events: 15798 (Vaccine), 24984 (Control)					
Heterogeneity: Tau² = 0.01; Chi² = 163.57, df = 12 (P<0.00001); I² =93%					
Test for overall effect: Z = 10.26 (P < 0.00001)					
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.99), I² =0.0%					

Analysis 2.1. Comparison 2 Inactivated vaccine versus placebo or no intervention (RCTs by age group), Outcome 1 Influenza.

Review: Vaccines for preventing influenza in healthy children

Comparison: 2 Inactivated vaccine versus placebo or no intervention (RCTs by age group)

Outcome: 1 Influenza

Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 under 2 years					
aa Hoberman 2003a	15/273	22/138		19.1 %	0.34 [0.18, 0.64]
aa Hoberman 2003b	9/252	4/123		8.1 %	1.10 [0.35, 3.50]
Subtotal (95% CI)	**525**	**261**		**27.2 %**	**0.55 [0.18, 1.69]**
Total events: 24 (Vaccine), 26 (Control)					
Heterogeneity: Tau² = 0.45; Chi² = 3.00, df = 1 (P = 0.08); I² =67%					
Test for overall effect: Z = 1.04 (P = 0.30)					
2 under 6 years					
aa Clover 1991	9/35	20/51		18.0 %	0.66 [0.34, 1.27]
aa Gruber 1990	3/19	9/27		8.0 %	0.47 [0.15, 1.52]
Subtotal (95% CI)	**54**	**78**		**25.9 %**	**0.61 [0.34, 1.08]**
Total events: 12 (Vaccine), 29 (Control)					
Heterogeneity: Tau² = 0.0; Chi² = 0.23, df = 1 (P = 0.63); I² =0.0%					
Test for overall effect: Z = 1.71 (P = 0.087)					
3 over 6 years					

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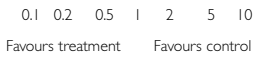
Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
aa Beutner 1979a	28/300	82/275		28.7 %	0.31 [0.21, 0.47]
aa Clover 1991	0/19	16/31		1.7 %	0.05 [0.00, 0.76]
aa Gruber 1990	7/35	28/50		16.5 %	0.36 [0.18, 0.72]
Subtotal (95% CI)	**354**	**356**		**46.9 %**	**0.31 [0.22, 0.45]**
Total events: 35 (Vaccine), 126 (Control)					
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.03$, df = 2 (P = 0.36); $I^2 = 2\%$					
Test for overall effect: Z = 6.46 (P < 0.00001)					
Total (95% CI)	**933**	**695**		**100.0 %**	**0.41 [0.29, 0.59]**
Total events: 71 (Vaccine), 181 (Control)					
Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 9.35$, df = 6 (P = 0.15); $I^2 = 36\%$					
Test for overall effect: Z = 4.76 (P < 0.00001)					
Test for subgroup differences: $Chi^2 = 4.12$, df = 2 (P = 0.13), $I^2 = 51\%$					



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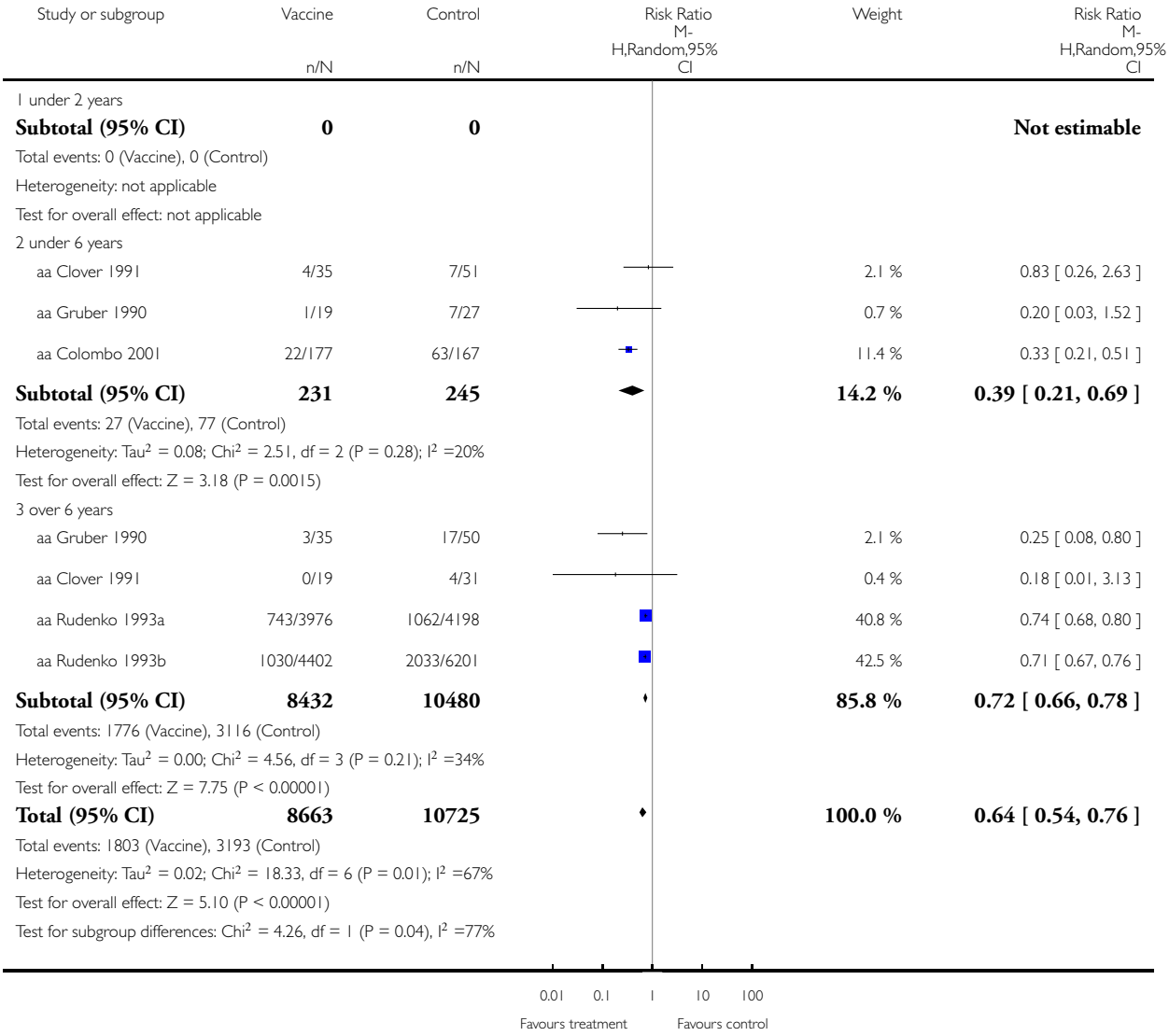
Analysis 2.2. Comparison 2 Inactivated vaccine versus placebo or no intervention (RCTs by age group), Outcome 2 Influenza-like illness.

Review: Vaccines for preventing influenza in healthy children

Comparison: 2 Inactivated vaccine versus placebo or no intervention (RCTs by age group)

Outcome: 2 Influenza-like illness



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Analysis 3.1. Comparison 3 Live attenuated vaccines (cohort studies by age group), Outcome 1 Influenza.

Review: Vaccines for preventing influenza in healthy children

Comparison: 3 Live attenuated vaccines (cohort studies by age group)

Outcome: 1 Influenza

Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 under 2 years					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Vaccine), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 under 6 years					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Vaccine), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
3 over 6 years					
ca Burtseva 1991	14/39	28/44		100.0 %	0.56 [0.35, 0.91]
Subtotal (95% CI)	**39**	**44**		**100.0 %**	**0.56 [0.35, 0.91]**
Total events: 14 (Vaccine), 28 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.36 (P = 0.018)					
Total (95% CI)	**39**	**44**		**100.0 %**	**0.56 [0.35, 0.91]**
Total events: 14 (Vaccine), 28 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.36 (P = 0.018)					
Test for subgroup differences: Not applicable					

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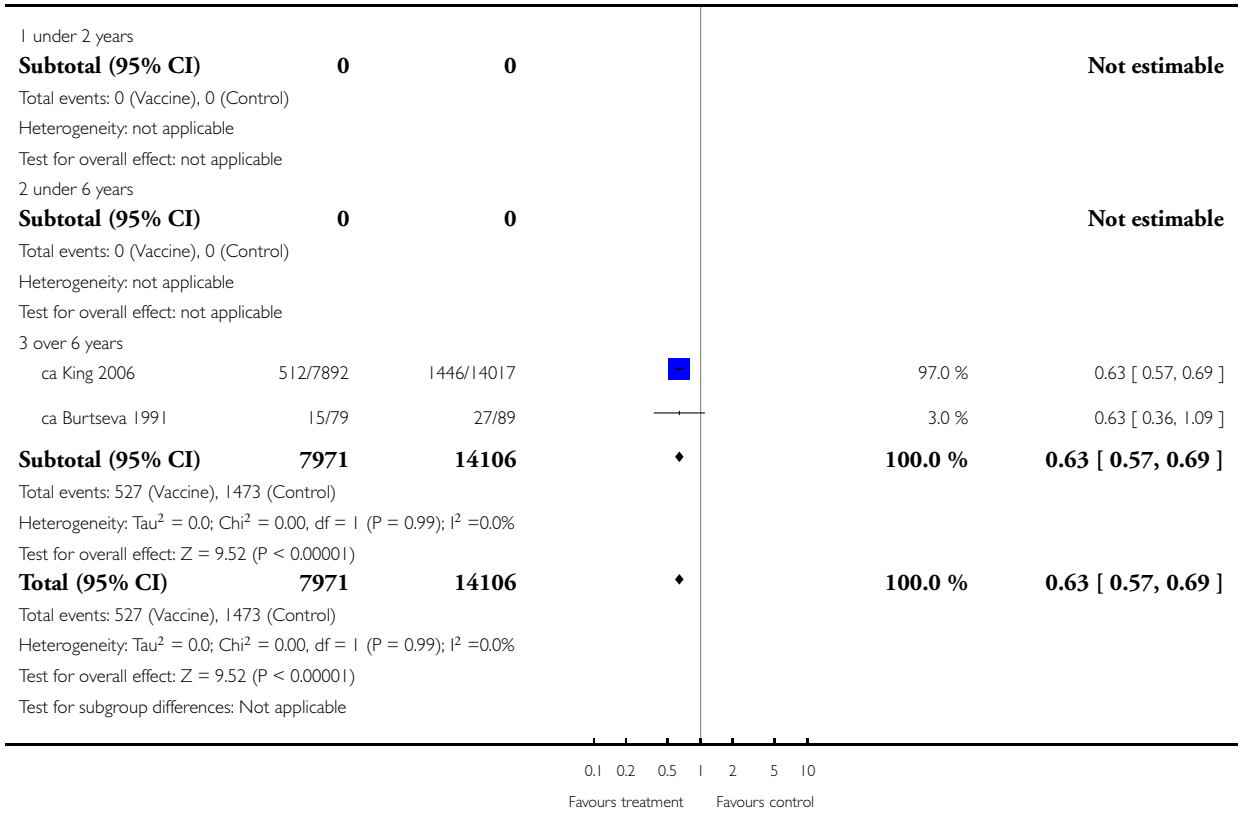
Analysis 3.2. Comparison 3 Live attenuated vaccines (cohort studies by age group), Outcome 2 Influenza-like illness.

Review: Vaccines for preventing influenza in healthy children

Comparison: 3 Live attenuated vaccines (cohort studies by age group)

Outcome: 2 Influenza-like illness

Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 under 2 years					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Vaccine), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 under 6 years					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Vaccine), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
3 over 6 years					
ca King 2006	512/7892	1446/14017		97.0 %	0.63 [0.57, 0.69]
ca Burtseva 1991	15/79	27/89		3.0 %	0.63 [0.36, 1.09]
Subtotal (95% CI)	**7971**	**14106**		**100.0 %**	**0.63 [0.57, 0.69]**
Total events: 527 (Vaccine), 1473 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.00$, df = 1 (P = 0.99); $I^2 = 0.0\%$					
Test for overall effect: Z = 9.52 (P < 0.00001)					
Total (95% CI)	**7971**	**14106**		**100.0 %**	**0.63 [0.57, 0.69]**
Total events: 527 (Vaccine), 1473 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.00$, df = 1 (P = 0.99); $I^2 = 0.0\%$					
Test for overall effect: Z = 9.52 (P < 0.00001)					
Test for subgroup differences: Not applicable					



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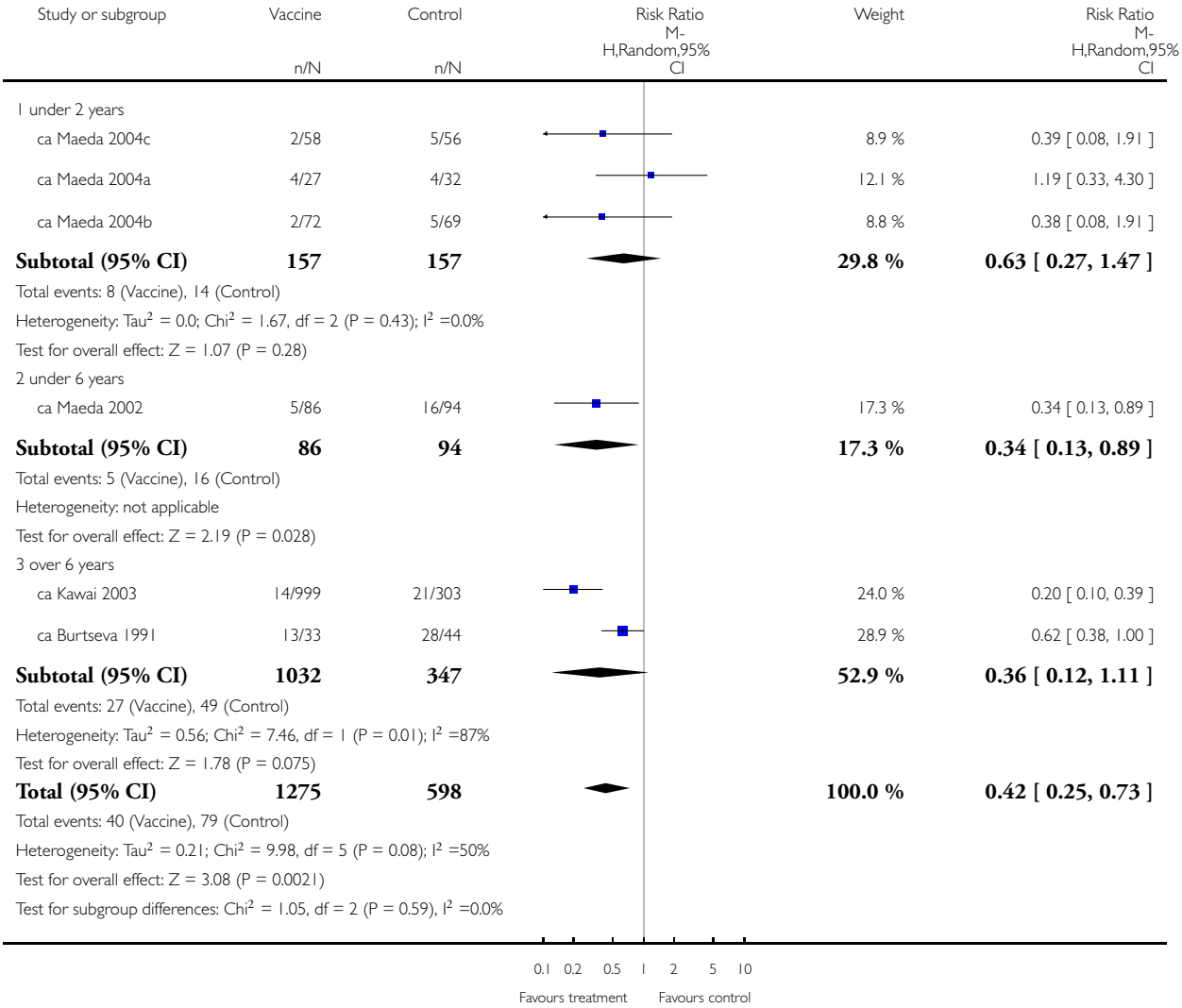
Analysis 4.1. Comparison 4 Inactivated vaccines (cohort studies by age group), Outcome 1 Influenza.

Review: Vaccines for preventing influenza in healthy children

Comparison: 4 Inactivated vaccines (cohort studies by age group)

Outcome: 1 Influenza



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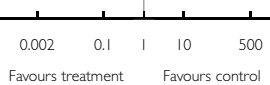
Analysis 4.2. Comparison 4 Inactivated vaccines (cohort studies by age group), Outcome 2 Influenza-like illness.

Review: Vaccines for preventing influenza in healthy children

Comparison: 4 Inactivated vaccines (cohort studies by age group)

Outcome: 2 Influenza-like illness

Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 under 2 years					
ca Yin 2011	4/9	14/14		6.4 %	0.47 [0.23, 0.93]
Subtotal (95% CI)	**9**	**14**		**6.4 %**	**0.47 [0.23, 0.93]**
Total events: 4 (Vaccine), 14 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.17 (P = 0.030)					
2 under 6 years					
ca Chumakov 1987	1469/2075	798/1109		14.3 %	0.98 [0.94, 1.03]
ca Jianping 1999	1/80	7/88		1.2 %	0.16 [0.02, 1.25]
ca Yin 2011	15/62	44/88		8.9 %	0.48 [0.30, 0.79]
ca Kawai 2003	12/474	16/157		6.1 %	0.25 [0.12, 0.51]
ca Fujieda 2006	623/1512	681/1401		14.1 %	0.85 [0.78, 0.92]
Subtotal (95% CI)	**4203**	**2843**		**44.6 %**	**0.74 [0.59, 0.93]**
Total events: 2120 (Vaccine), 1546 (Control)					
Heterogeneity: Tau^2 = 0.03; Chi^2 = 35.87, df = 4 (P<0.00001); I^2 =89%					
Test for overall effect: Z = 2.60 (P = 0.0093)					
3 over 6 years					
ca El'shina 2000	146/930	620/2220		13.4 %	0.56 [0.48, 0.66]
ca Slobodniuk 2002c	5/80	14/80		4.2 %	0.36 [0.13, 0.94]
ca Slobodniuk 2002a	10/106	13/106		5.6 %	0.77 [0.35, 1.68]
ca Kawai 2003	9/525	25/146		6.0 %	0.10 [0.05, 0.21]
ca Burtseva 1991	10/57	27/89		6.9 %	0.58 [0.30, 1.10]
ca Slobodniuk 2002b	5/96	12/96		4.0 %	0.42 [0.15, 1.14]
ca Vasil'eva 1982	23/183	30/152		8.8 %	0.64 [0.39, 1.05]
Subtotal (95% CI)	**1977**	**2889**		**48.9 %**	**0.44 [0.29, 0.68]**
Total events: 208 (Vaccine), 741 (Control)					
Heterogeneity: Tau^2 = 0.21; Chi^2 = 22.34, df = 6 (P = 0.001); I^2 =73%					
Test for overall effect: Z = 3.78 (P = 0.00016)					
Total (95% CI)	**6189**	**5746**		**100.0 %**	**0.53 [0.42, 0.67]**



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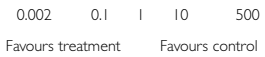
Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Total events: 2332 (Vaccine), 2301 (Control)					
Heterogeneity: Tau² = 0.10; Chi² = 136.71, df = 12 (P<0.00001); I² =91%					
Test for overall effect: Z = 5.24 (P < 0.00001)					
Test for subgroup differences: Chi² = 5.25, df = 2 (P = 0.07), I² =62%					



Analysis 4.3. Comparison 4 Inactivated vaccines (cohort studies by age group), Outcome 3 Otitis media.

Review: Vaccines for preventing influenza in healthy children

Comparison: 4 Inactivated vaccines (cohort studies by age group)

Outcome: 3 Otitis media

Study or subgroup	Vaccine n/N	Standard care n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Children aged 6 months to 5 years					
ca Ozgur 2006	8/61	16/58		100.0 %	0.48 [0.22, 1.03]
Total (95% CI)	**61**	**58**		**100.0 %**	**0.48 [0.22, 1.03]**
Total events: 8 (Vaccine), 16 (Standard care)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.90 (P = 0.058)					
Test for subgroup differences: Not applicable					

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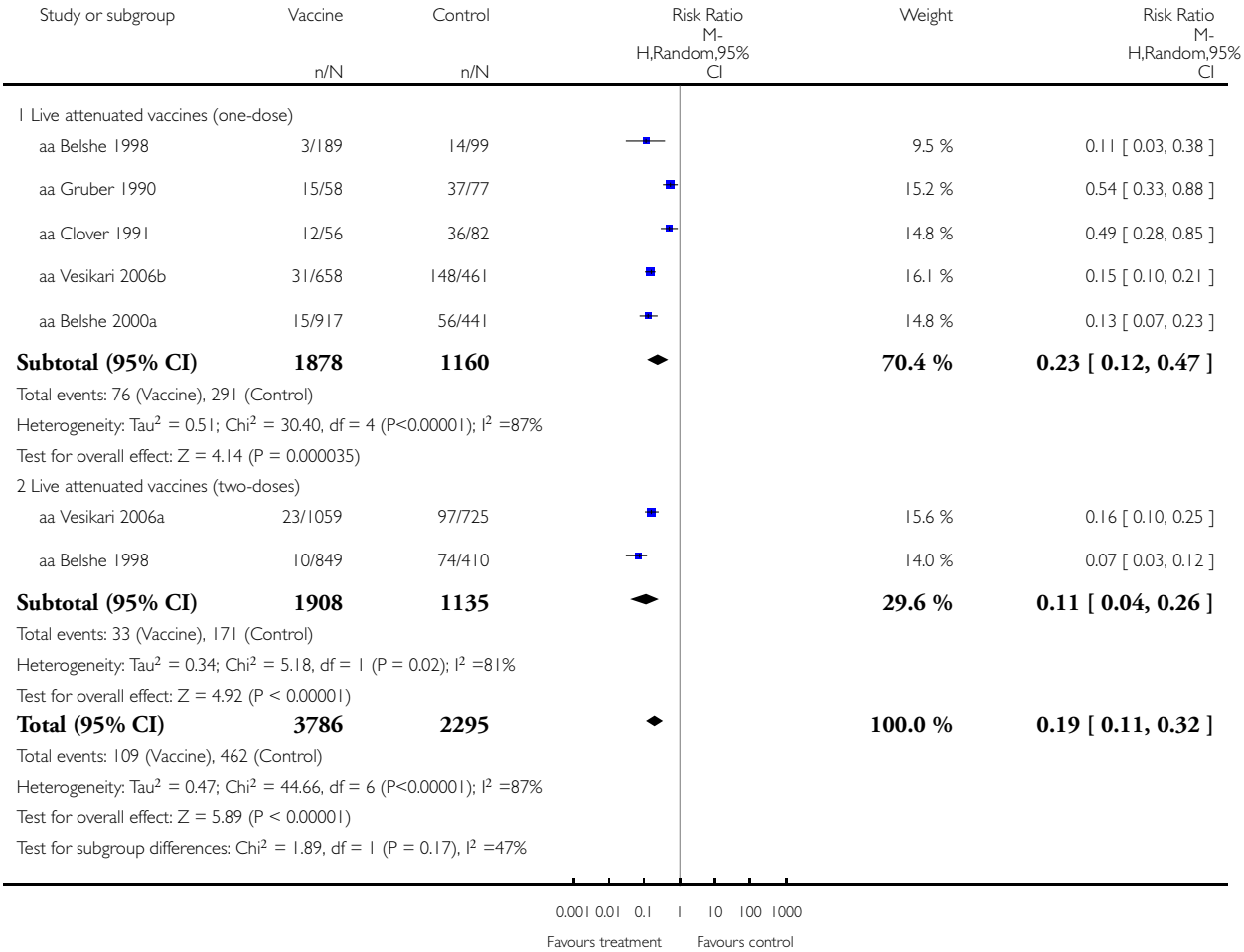
Analysis 5.1. Comparison 5 Live vaccine versus placebo (RCTs), Outcome 1 Influenza.

Review: Vaccines for preventing influenza in healthy children

Comparison: 5 Live vaccine versus placebo (RCTs)

Outcome: 1 Influenza



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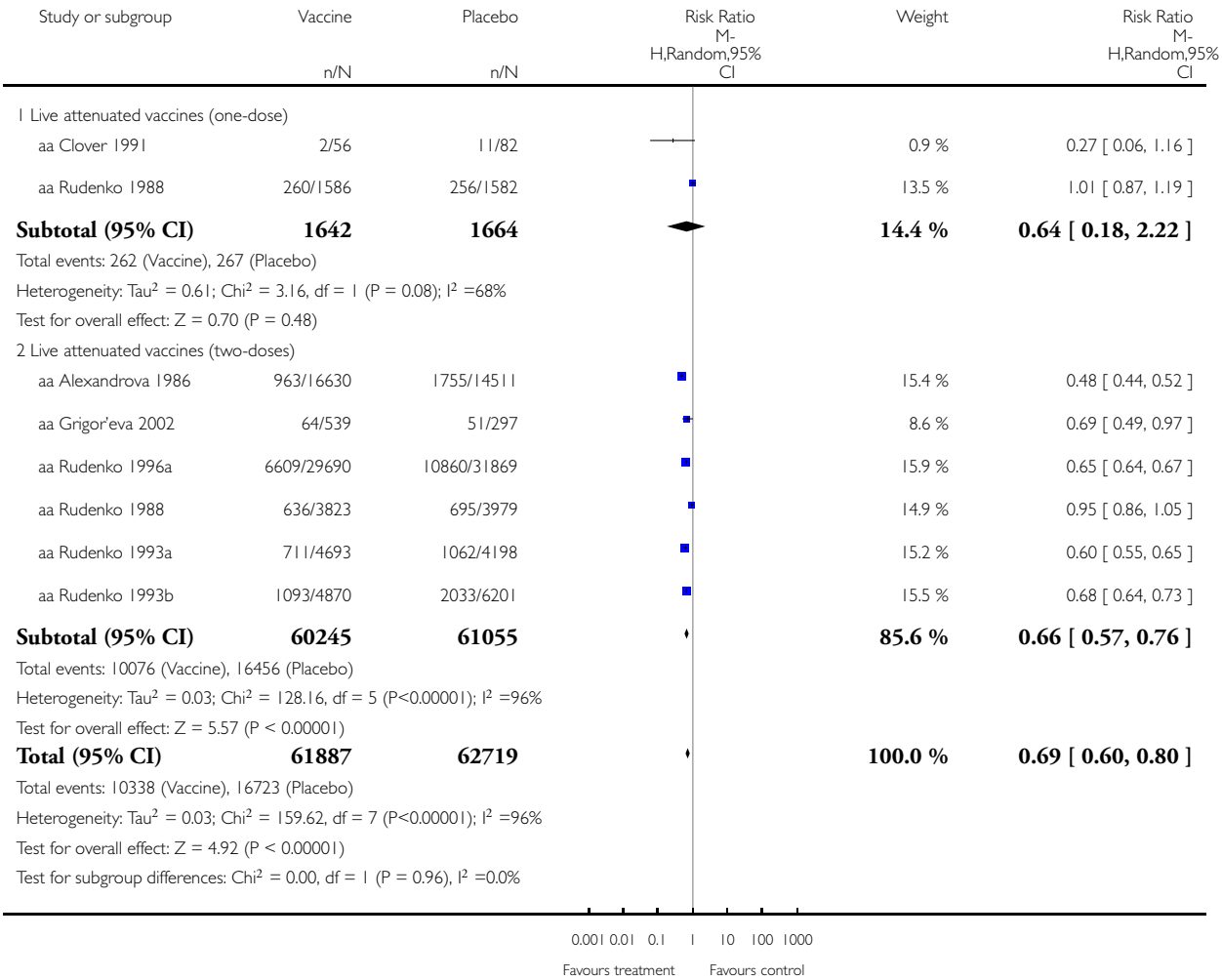
Analysis 5.2. Comparison 5 Live vaccine versus placebo (RCTs), Outcome 2 Influenza-like illness.

Review: Vaccines for preventing influenza in healthy children

Comparison: 5 Live vaccine versus placebo (RCTs)

Outcome: 2 Influenza-like illness



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Analysis 5.3. Comparison 5 Live vaccine versus placebo (RCTs), Outcome 3 Otitis media (all episodes).

Review: Vaccines for preventing influenza in healthy children

Comparison: 5 Live vaccine versus placebo (RCTs)

Outcome: 3 Otitis media (all episodes)

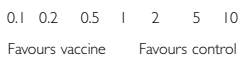
Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
aa Vesikari 2006a	951/1059	664/725		99.0 %	0.98 [0.95, 1.01]
aa Vesikari 2006b	90/639	60/450		1.0 %	1.06 [0.78, 1.43]
Total (95% CI)	**1698**	**1175**		**100.0 %**	**0.98 [0.95, 1.01]**

Total events: 1041 (Vaccine), 724 (Control)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.36$, df = 1 (P = 0.55); $I^2 = 0.0\%$

Test for overall effect: Z = 1.25 (P = 0.21)

Test for subgroup differences: Not applicable



Analysis 5.4. Comparison 5 Live vaccine versus placebo (RCTs), Outcome 4 Working days lost (number of events, parents).

Review: Vaccines for preventing influenza in healthy children

Comparison: 5 Live vaccine versus placebo (RCTs)

Outcome: 4 Working days lost (number of events, parents)

Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
aa Vesikari 2006a	247/1059	203/725		53.2 %	0.83 [0.71, 0.98]
aa Vesikari 2006b	82/640	105/450		46.8 %	0.55 [0.42, 0.71]
Total (95% CI)	**1699**	**1175**		**100.0 %**	**0.69 [0.46, 1.03]**

Total events: 329 (Vaccine), 308 (Control)

Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 7.08$, df = 1 (P = 0.01); $I^2 = 86\%$

Test for overall effect: Z = 1.81 (P = 0.070)

Test for subgroup differences: Not applicable

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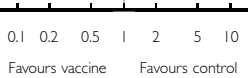
Analysis 5.5. Comparison 5 Live vaccine versus placebo (RCTs), Outcome 5 Drug prescriptions (number of events).

Review: Vaccines for preventing influenza in healthy children

Comparison: 5 Live vaccine versus placebo (RCTs)

Outcome: 5 Drug prescriptions (number of events)

Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
aa Vesikari 2006a	376/1059	261/725		100.0 %	0.99 [0.87, 1.12]
Total (95% CI)	**1059**	**725**		**100.0 %**	**0.99 [0.87, 1.12]**
Total events: 376 (Vaccine), 261 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.21 (P = 0.83)					
Test for subgroup differences: Not applicable					



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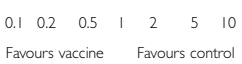
Analysis 5.6. Comparison 5 Live vaccine versus placebo (RCTs), Outcome 6 Outpatients attendance for pneumonia and influenza.

Review: Vaccines for preventing influenza in healthy children

Comparison: 5 Live vaccine versus placebo (RCTs)

Outcome: 6 Outpatients attendance for pneumonia and influenza

Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
aa Vesikari 2006a	361/1059	292/725		60.7 %	0.85 [0.75, 0.96]
aa Vesikari 2006b	84/640	91/450		39.3 %	0.65 [0.49, 0.85]
Total (95% CI)	**1699**	**1175**		**100.0 %**	**0.76 [0.59, 0.98]**
Total events: 445 (Vaccine), 383 (Control)					
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 3.11$, df = 1 (P = 0.08); $I^2 = 68\%$					
Test for overall effect: Z = 2.08 (P = 0.038)					
Test for subgroup differences: Not applicable					



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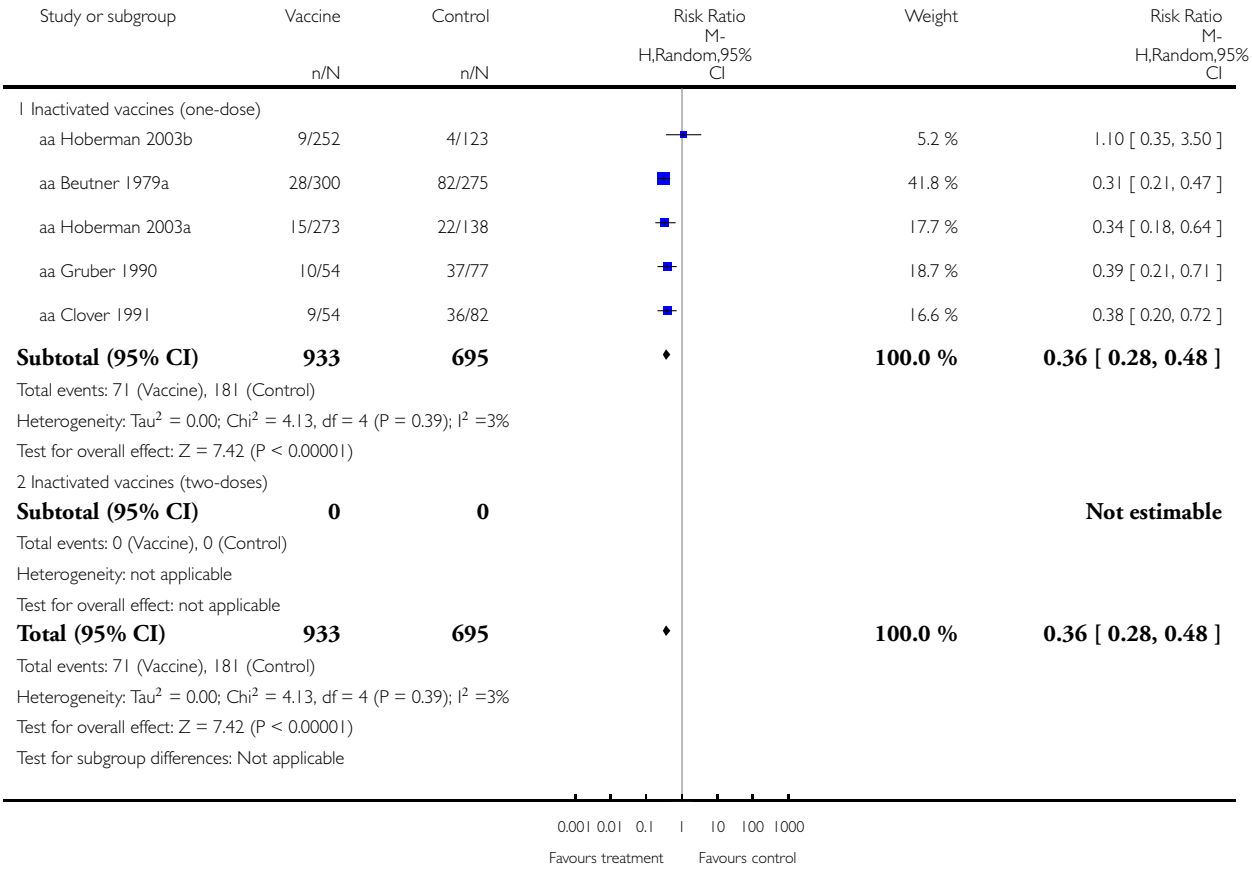
Analysis 6.1. Comparison 6 Inactivated vaccine versus placebo (RCTs), Outcome 1 Influenza.

Review: Vaccines for preventing influenza in healthy children

Comparison: 6 Inactivated vaccine versus placebo (RCTs)

Outcome: 1 Influenza



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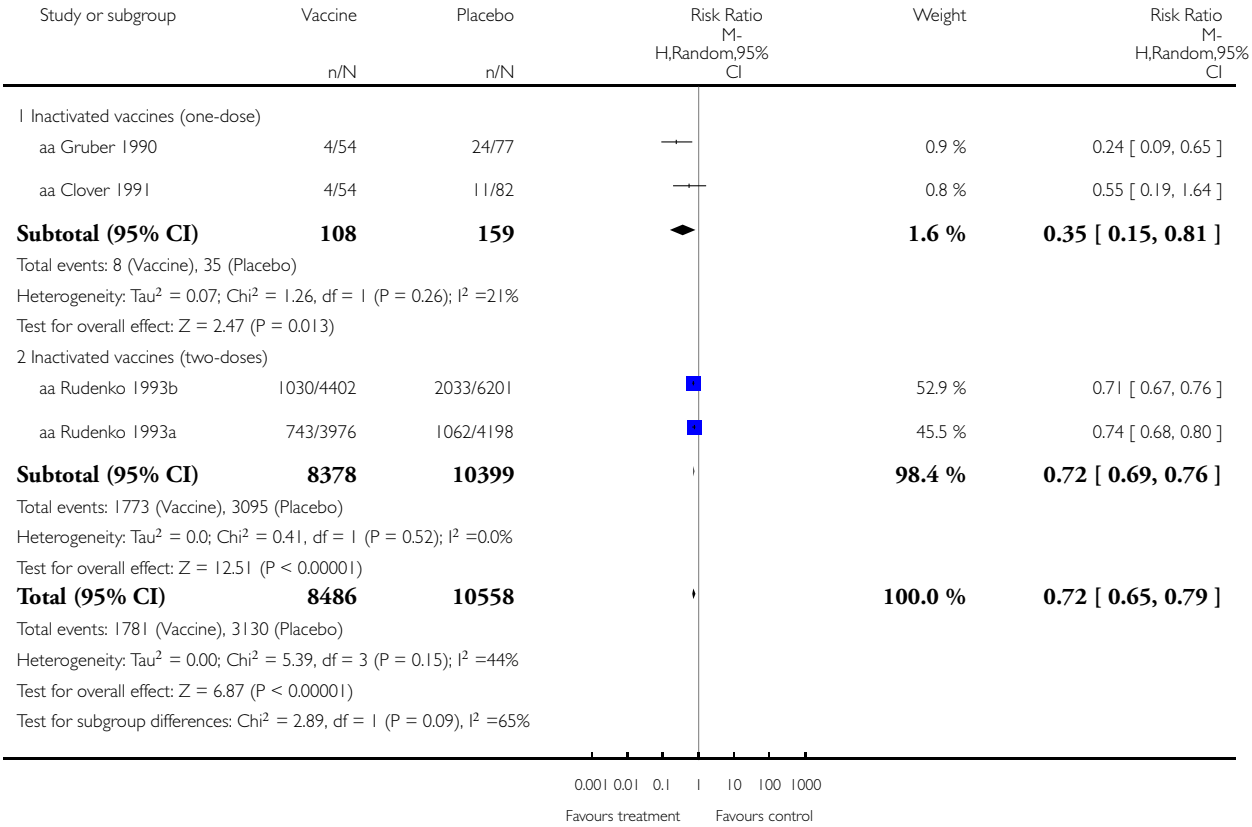
Analysis 6.2. Comparison 6 Inactivated vaccine versus placebo (RCTs), Outcome 2 Influenza-like illness.

Review: Vaccines for preventing influenza in healthy children

Comparison: 6 Inactivated vaccine versus placebo (RCTs)

Outcome: 2 Influenza-like illness



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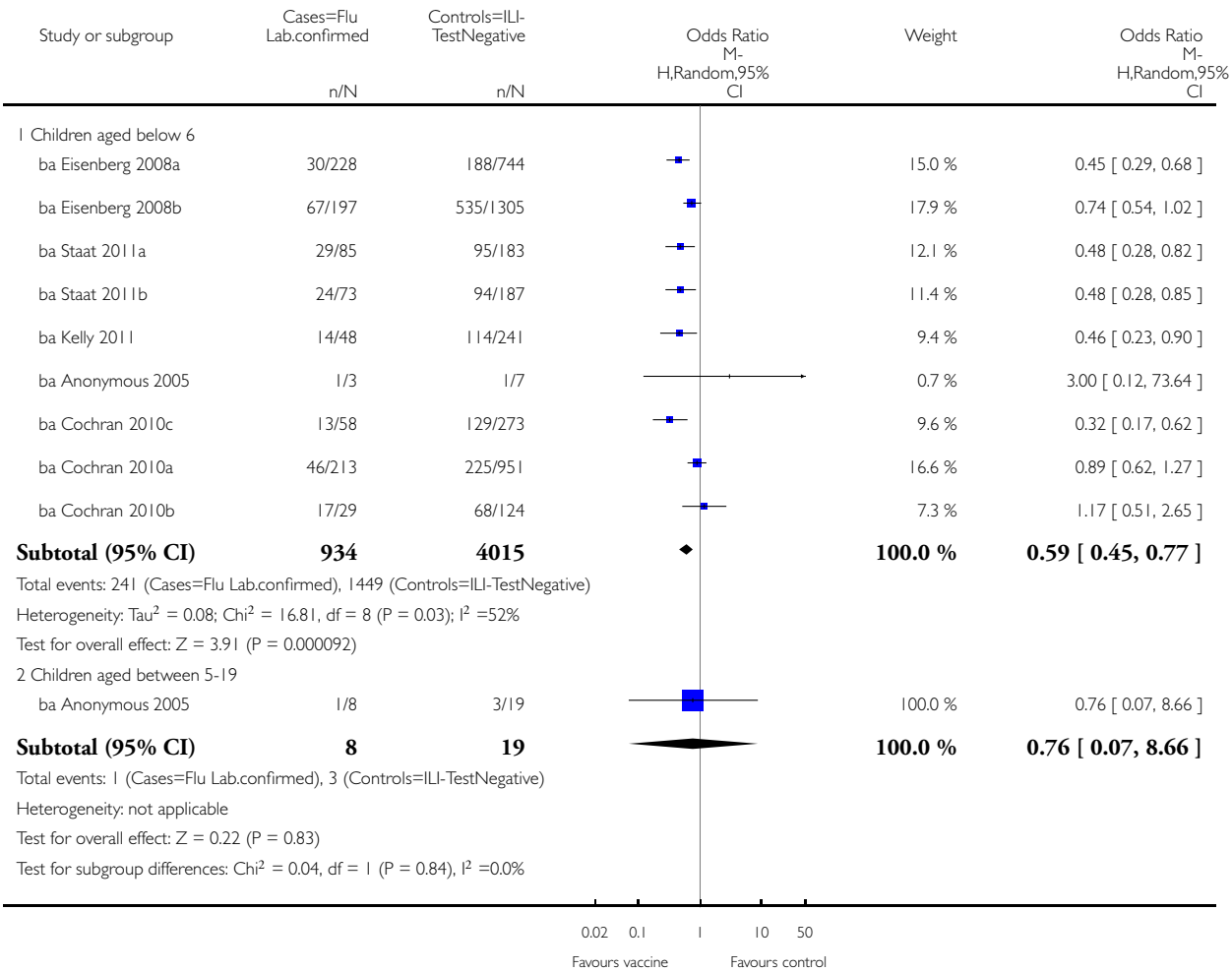
Analysis 7.1. Comparison 7 Case-control studies, Outcome 1 Influenza vs influenza-like illness (crude data).

Review: Vaccines for preventing influenza in healthy children

Comparison: 7 Case-control studies

Outcome: 1 Influenza vs influenza-like illness (crude data)



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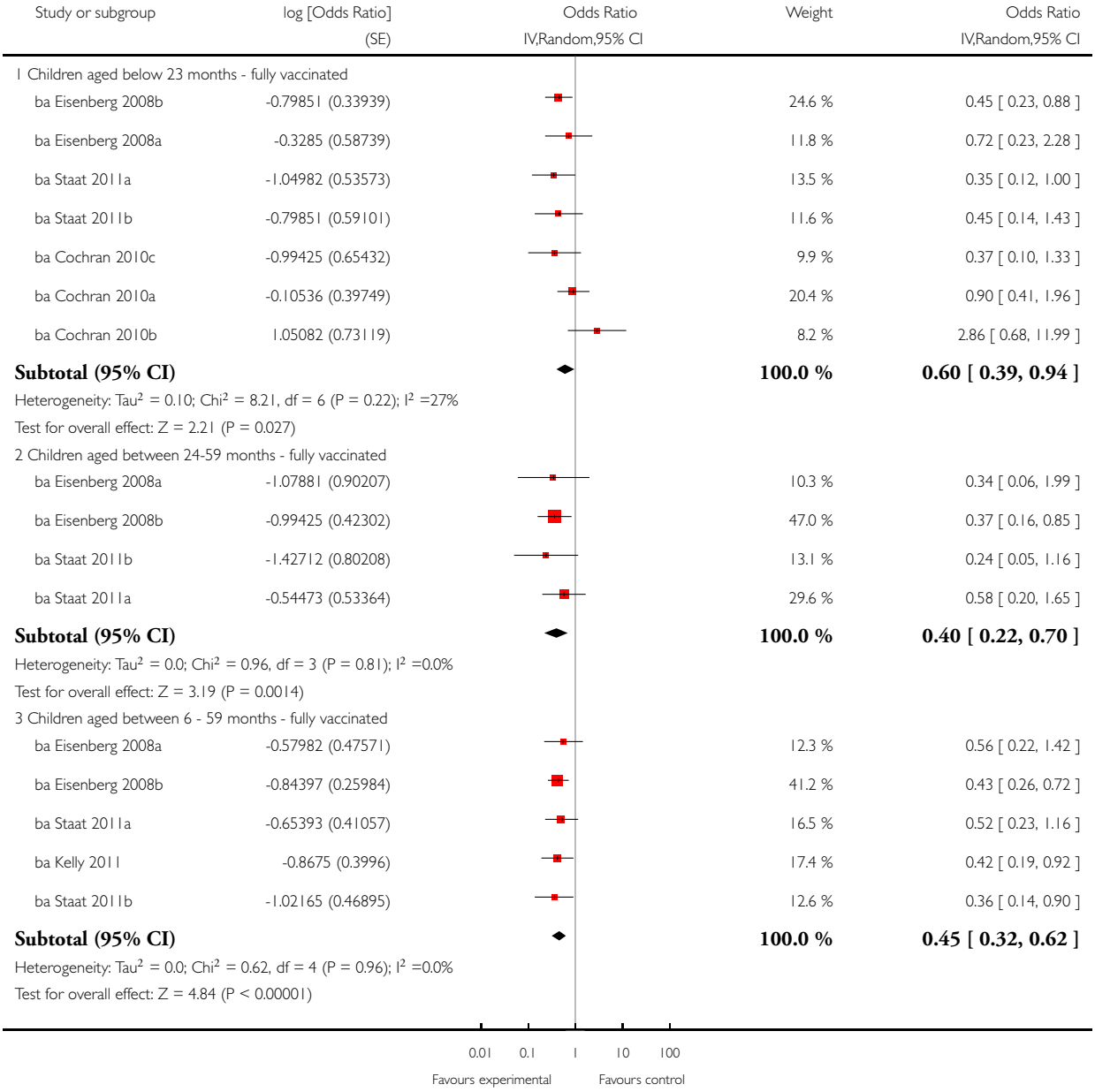
Analysis 7.2. Comparison 7 Case-control studies, Outcome 2 Influenza vs influenza-like illness (adj. estimates).

Review: Vaccines for preventing influenza in healthy children

Comparison: 7 Case-control studies

Outcome: 2 Influenza vs influenza-like illness (adj. estimates)



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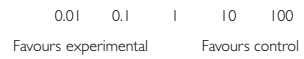
Study or subgroup	log [Odds Ratio] (SE)	Odds Ratio IV,Random,95% CI	Weight	Odds Ratio IV,Random,95% CI
4 Children aged below 14 years old - fully vaccinated				
ba Kissling 2011	-1.47841 (0.66486)		100.0 %	0.23 [0.06, 0.84]
Subtotal (95% CI)			**100.0 %**	**0.23 [0.06, 0.84]**
Heterogeneity: not applicable				
Test for overall effect: Z = 2.22 (P = 0.026)				
Test for subgroup differences: Chi^2 = 2.85, df = 3 (P = 0.42), I^2 =0.0%				



Analysis 7.3. Comparison 7 Case-control studies, Outcome 3 Influenza-like illness vs no symptoms.

Review: Vaccines for preventing influenza in healthy children

Comparison: 7 Case-control studies

Outcome: 3 Influenza-like illness vs no symptoms

Study or subgroup	Vaccine n/N	Control n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 Inactivated vaccine (one-dose)					
ba Hirota 1992	12/48	76/196		62.2 %	0.53 [0.26, 1.07]
Subtotal (95% CI)	**48**	**196**		**62.2 %**	**0.53 [0.26, 1.07]**
Total events: 12 (Vaccine), 76 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.76 (P = 0.078)					
2 Inactivated vaccine (two-doses)					
ba Hirota 1992	6/48	48/196		37.8 %	0.44 [0.18, 1.10]
Subtotal (95% CI)	**48**	**196**		**37.8 %**	**0.44 [0.18, 1.10]**
Total events: 6 (Vaccine), 48 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.76 (P = 0.079)					
Total (95% CI)	**96**	**392**		**100.0 %**	**0.49 [0.28, 0.86]**
Total events: 18 (Vaccine), 124 (Control)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.09, df = 1 (P = 0.76); I^2 =0.0%					
Test for overall effect: Z = 2.47 (P = 0.014)					
Test for subgroup differences: Chi^2 = 0.09, df = 1 (P = 0.76), I^2 =0.0%					

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Analysis 8.1. Comparison 8 Vaccine versus placebo, Outcome 1 Influenza.

Review: Vaccines for preventing influenza in healthy children

Comparison: 8 Vaccine versus placebo

Outcome: 1 Influenza

Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Live attenuated vaccines (one-dose)					
aa Belshe 1998	3/189	14/99		5.9 %	0.11 [0.03, 0.38]
aa Belshe 2000a	15/917	56/441		9.7 %	0.13 [0.07, 0.23]
aa Clover 1991	12/56	36/82		9.7 %	0.49 [0.28, 0.85]
aa Gruber 1990	15/58	37/77		10.1 %	0.54 [0.33, 0.88]
Subtotal (95% CI)	**1220**	**699**		**35.5 %**	**0.27 [0.12, 0.61]**
Total events: 45 (Vaccine), 143 (Control)					
Heterogeneity: Tau^2 = 0.57; Chi^2 = 20.17, df = 3 (P = 0.00016); I^2 =85%					
Test for overall effect: Z = 3.14 (P = 0.0017)					
2 Live attenuated vaccines (two-doses)					
aa Belshe 1998	10/849	74/410		9.2 %	0.07 [0.03, 0.12]
aa Vesikari 2006a	23/1059	97/725		10.4 %	0.16 [0.10, 0.25]
Subtotal (95% CI)	**1908**	**1135**		**19.6 %**	**0.11 [0.04, 0.26]**
Total events: 33 (Vaccine), 171 (Control)					
Heterogeneity: Tau^2 = 0.34; Chi^2 = 5.18, df = 1 (P = 0.02); I^2 =81%					
Test for overall effect: Z = 4.92 (P < 0.00001)					
3 Inactivated vaccines (one-dose)					
aa Beutner 1979a	28/300	82/275		10.6 %	0.31 [0.21, 0.47]
aa Clover 1991	9/54	36/82		9.2 %	0.38 [0.20, 0.72]
aa Gruber 1990	10/54	37/77		9.5 %	0.39 [0.21, 0.71]
aa Hoberman 2003a	15/273	22/138		9.3 %	0.34 [0.18, 0.64]
aa Hoberman 2003b	9/252	4/123		6.2 %	1.10 [0.35, 3.50]
Subtotal (95% CI)	**933**	**695**		**44.9 %**	**0.36 [0.28, 0.48]**
Total events: 71 (Vaccine), 181 (Control)					

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Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.13$, df = 4 (P = 0.39); $I^2 = 3\%$					
Test for overall effect: Z = 7.42 (P < 0.00001)					
4 Inactivated vaccines (two-doses)					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Vaccine), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**4061**	**2529**	◆	**100.0 %**	**0.27 [0.18, 0.42]**
Total events: 149 (Vaccine), 495 (Control)					
Heterogeneity: $Tau^2 = 0.39$; $Chi^2 = 54.65$, df = 10 (P<0.00001); $I^2 = 82\%$					
Test for overall effect: Z = 6.04 (P < 0.00001)					
Test for subgroup differences: $Chi^2 = 6.96$, df = 2 (P = 0.03), $I^2 = 71\%$					

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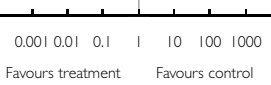
Analysis 8.2. Comparison 8 Vaccine versus placebo, Outcome 2 Influenza-like illness.

Review: Vaccines for preventing influenza in healthy children

Comparison: 8 Vaccine versus placebo

Outcome: 2 Influenza-like illness

Study or subgroup	Vaccine n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Live attenuated vaccines (one-dose)					
aa Clover 1991	2/56	11/82		0.5 %	0.27 [0.06, 1.16]
aa Rudenko 1988	260/1586	256/1582		9.9 %	1.01 [0.87, 1.19]
Subtotal (95% CI)	**1642**	**1664**		**10.4 %**	**0.64 [0.18, 2.22]**
Total events: 262 (Vaccine), 267 (Placebo)					
Heterogeneity: Tau^2 = 0.61; Chi^2 = 3.16, df = 1 (P = 0.08); I^2 =68%					
Test for overall effect: Z = 0.70 (P = 0.48)					
2 Live attenuated vaccines (two-doses)					
aa Alexandrova 1986	963/16630	1755/14511		11.7 %	0.48 [0.44, 0.52]
aa Grigor'eva 2002	64/539	51/297		5.7 %	0.69 [0.49, 0.97]
aa Rudenko 1996a	6609/29690	10860/31869		12.2 %	0.65 [0.64, 0.67]
aa Rudenko 1993b	1093/4870	2033/6201		11.8 %	0.68 [0.64, 0.73]
aa Rudenko 1988	636/3823	695/3979		11.2 %	0.95 [0.86, 1.05]
aa Rudenko 1993a	711/4693	1062/4198		11.5 %	0.60 [0.55, 0.65]
Subtotal (95% CI)	**60245**	**61055**		**64.2 %**	**0.66 [0.57, 0.76]**
Total events: 10076 (Vaccine), 16456 (Placebo)					
Heterogeneity: Tau^2 = 0.03; Chi^2 = 128.16, df = 5 (P<0.00001); I^2 =96%					
Test for overall effect: Z = 5.57 (P < 0.00001)					
3 Inactivated vaccines (one-dose)					
aa Clover 1991	4/54	11/82		1.0 %	0.55 [0.19, 1.64]
aa Gruber 1990	4/54	24/77		1.1 %	0.24 [0.09, 0.65]
Subtotal (95% CI)	**108**	**159**		**2.1 %**	**0.35 [0.15, 0.81]**
Total events: 8 (Vaccine), 35 (Placebo)					
Heterogeneity: Tau^2 = 0.07; Chi^2 = 1.26, df = 1 (P = 0.26); I^2 =21%					
Test for overall effect: Z = 2.47 (P = 0.013)					
4 Inactivated vaccines (two-doses)					
aa Rudenko 1993b	1030/4402	2033/6201		11.8 %	0.71 [0.67, 0.76]
aa Rudenko 1993a	743/3976	1062/4198		11.5 %	0.74 [0.68, 0.80]
Subtotal (95% CI)	**8378**	**10399**		**23.3 %**	**0.72 [0.69, 0.76]**
Total events: 1773 (Vaccine), 3095 (Placebo)					



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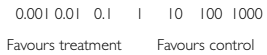
Study or subgroup	Vaccine n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.41, df = 1 (P = 0.52); I^2 =0.0%					
Test for overall effect: Z = 12.51 (P < 0.00001)					
Total (95% CI)	**70373**	**73277**		**100.0 %**	**0.69 [0.62, 0.77]**
Total events: 12119 (Vaccine), 19853 (Placebo)					
Heterogeneity: Tau^2 = 0.03; Chi^2 = 176.94, df = 11 (P<0.00001); I^2 =94%					
Test for overall effect: Z = 6.54 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 4.22, df = 3 (P = 0.24), I^2 =29%					



Analysis 8.3. Comparison 8 Vaccine versus placebo, Outcome 3 Secondary cases.

Review: Vaccines for preventing influenza in healthy children

Comparison: 8 Vaccine versus placebo

Outcome: 3 Secondary cases

Study or subgroup	Vaccine n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Live attenuated vaccines (one-dose)					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Vaccine), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Live attenuated vaccines (two-doses)					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Vaccine), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
3 Inactivated vaccines (one-dose)					
aa Gruber 1990	7/56	5/67		100.0 %	1.68 [0.56, 4.99]
Subtotal (95% CI)	**56**	**67**		**100.0 %**	**1.68 [0.56, 4.99]**
Total events: 7 (Vaccine), 5 (Placebo)					

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Study or subgroup	Vaccine n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Heterogeneity: not applicable					
Test for overall effect: Z = 0.93 (P = 0.35)					
4 Inactivated vaccines (two-doses)					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Vaccine), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**56**	**67**		**100.0 %**	**1.68 [0.56, 4.99]**
Total events: 7 (Vaccine), 5 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.93 (P = 0.35)					
Test for subgroup differences: Not applicable					

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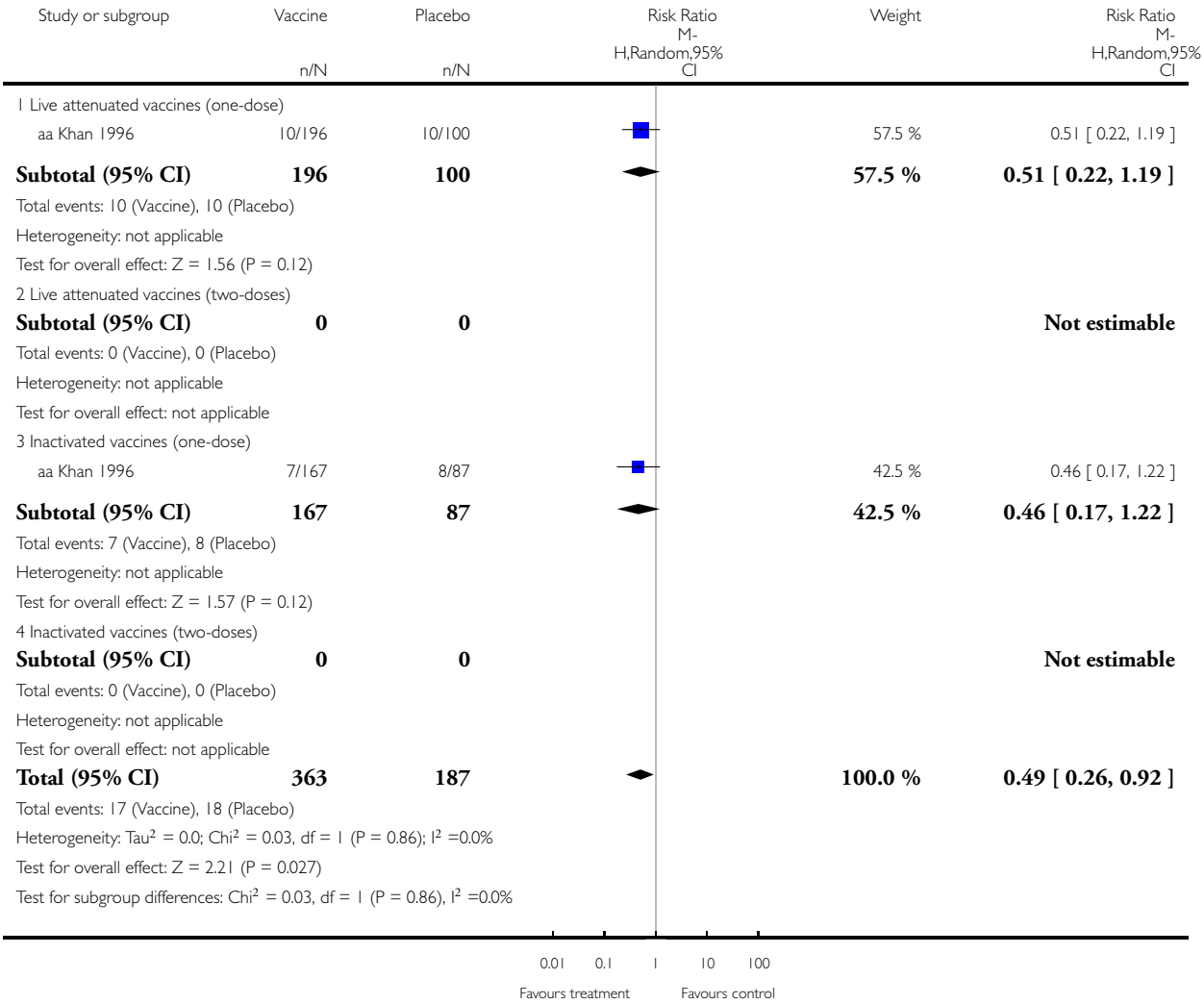
Analysis 8.4. Comparison 8 Vaccine versus placebo, Outcome 4 School absenteeism.

Review: Vaccines for preventing influenza in healthy children

Comparison: 8 Vaccine versus placebo

Outcome: 4 School absenteeism



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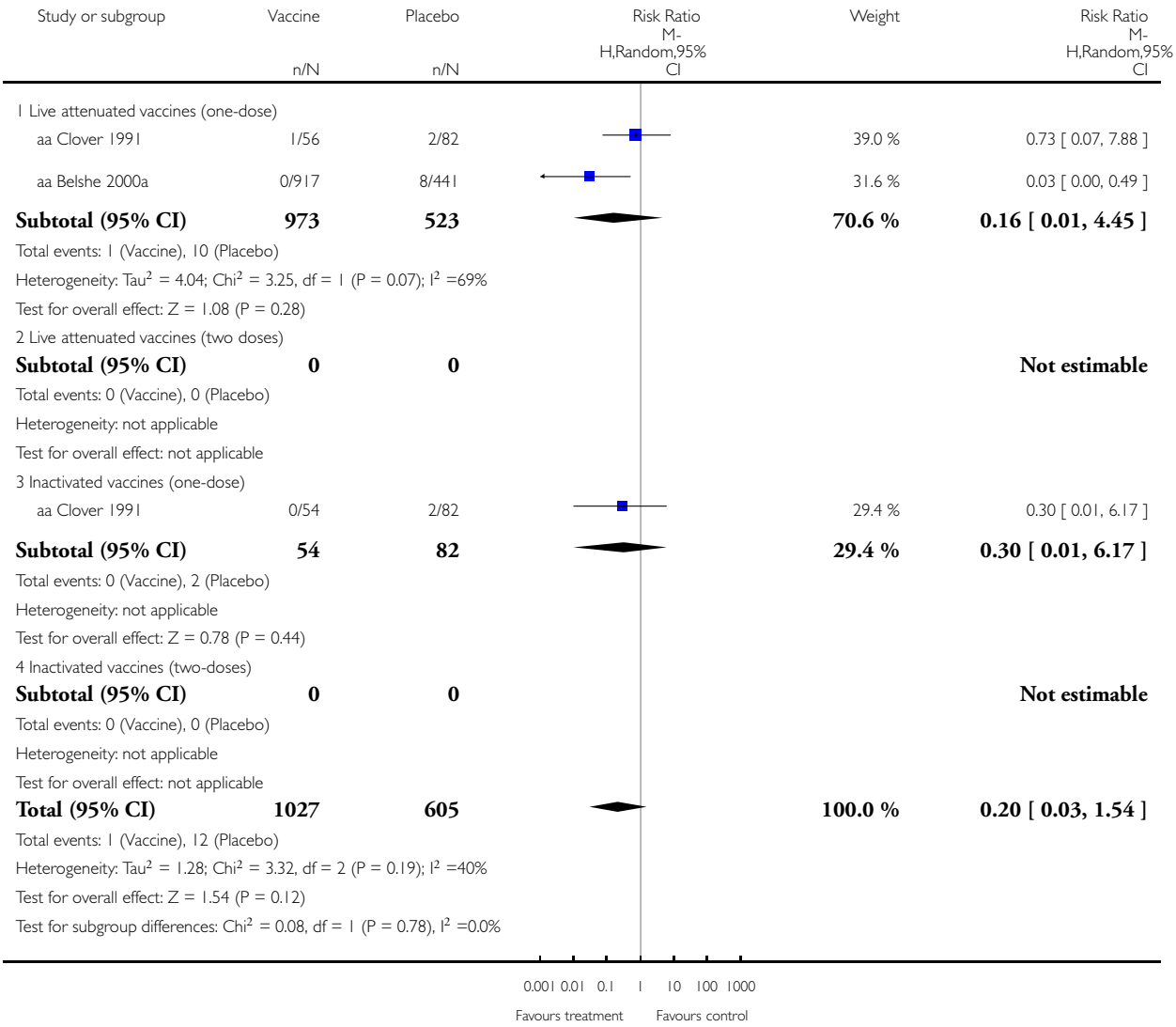
Analysis 8.5. Comparison 8 Vaccine versus placebo, Outcome 5 Lower respiratory tract disease.

Review: Vaccines for preventing influenza in healthy children

Comparison: 8 Vaccine versus placebo

Outcome: 5 Lower respiratory tract disease



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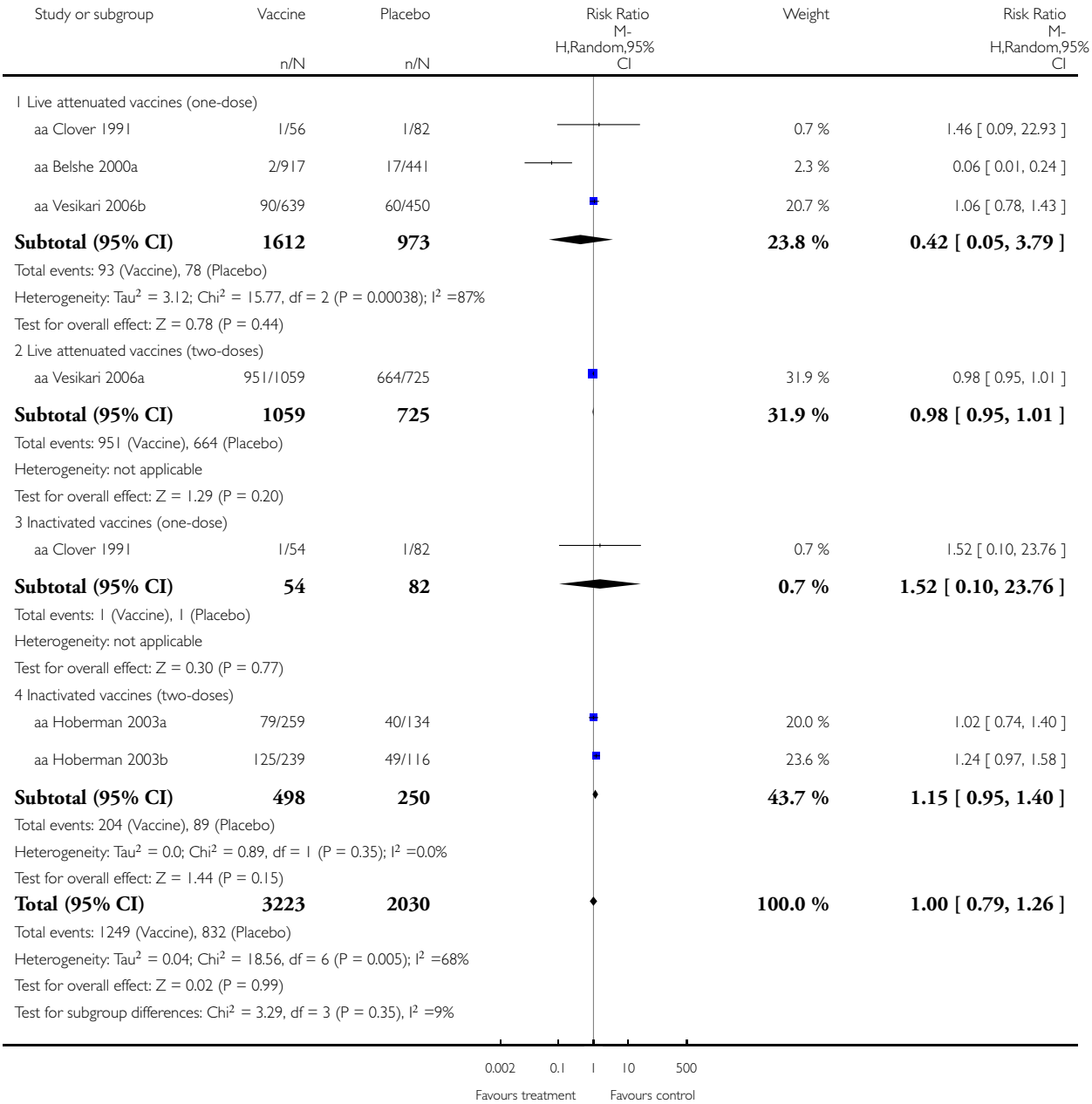
Analysis 8.6. Comparison 8 Vaccine versus placebo, Outcome 6 Acute otitis media.

Review: Vaccines for preventing influenza in healthy children

Comparison: 8 Vaccine versus placebo

Outcome: 6 Acute otitis media



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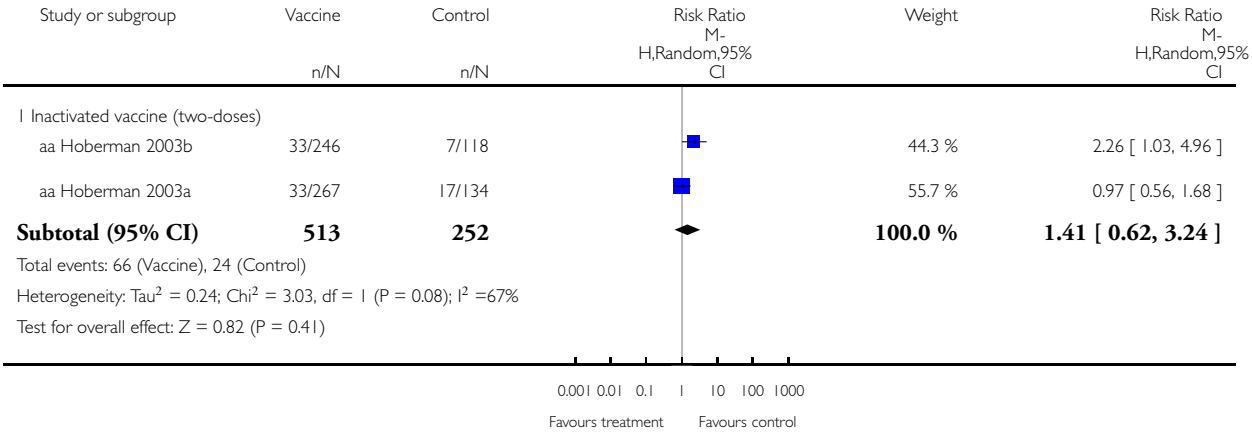
Analysis 8.7. Comparison 8 Vaccine versus placebo, Outcome 7 Hospitalisation due to acute otitis media.

Review: Vaccines for preventing influenza in healthy children

Comparison: 8 Vaccine versus placebo

Outcome: 7 Hospitalisation due to acute otitis media



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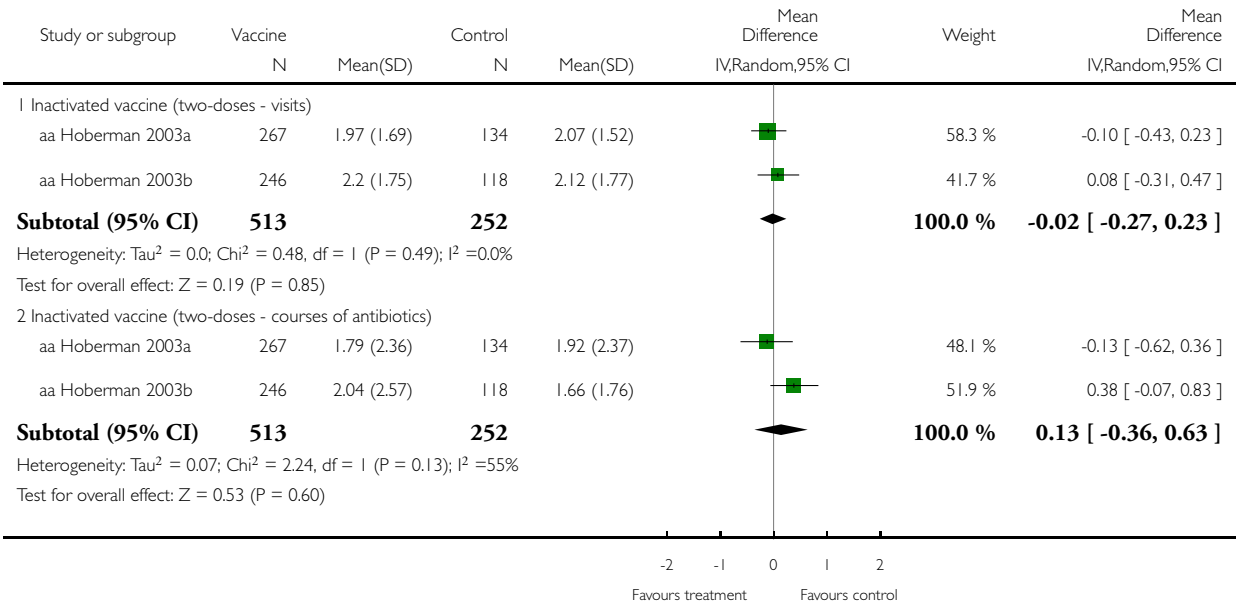
Analysis 8.8. Comparison 8 Vaccine versus placebo, Outcome 8 Consequences of acute otitis media.

Review: Vaccines for preventing influenza in healthy children

Comparison: 8 Vaccine versus placebo

Outcome: 8 Consequences of acute otitis media



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Analysis 8.9. Comparison 8 Vaccine versus placebo, Outcome 9 Outpatients attendance for pneumonia and influenza.

Review: Vaccines for preventing influenza in healthy children

Comparison: 8 Vaccine versus placebo

Outcome: 9 Outpatients attendance for pneumonia and influenza

Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Live attenuated vaccine (one-dose)					
aa Vesikari 2006b	84/640	91/450		39.3 %	0.65 [0.49, 0.85]
Subtotal (95% CI)	**640**	**450**		**39.3 %**	**0.65 [0.49, 0.85]**
Total events: 84 (Vaccine), 91 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.13 (P = 0.0018)					
2 Live attenuated vaccine (two-doses)					
aa Vesikari 2006a	361/1059	292/725		60.7 %	0.85 [0.75, 0.96]
Subtotal (95% CI)	**1059**	**725**		**60.7 %**	**0.85 [0.75, 0.96]**
Total events: 361 (Vaccine), 292 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.68 (P = 0.0073)					
Total (95% CI)	**1699**	**1175**		**100.0 %**	**0.76 [0.59, 0.98]**
Total events: 445 (Vaccine), 383 (Control)					
Heterogeneity: Tau^2 = 0.02; Chi^2 = 3.11, df = 1 (P = 0.08); I^2 =68%					
Test for overall effect: Z = 2.08 (P = 0.038)					
Test for subgroup differences: Chi^2 = 3.07, df = 1 (P = 0.08), I^2 =67%					

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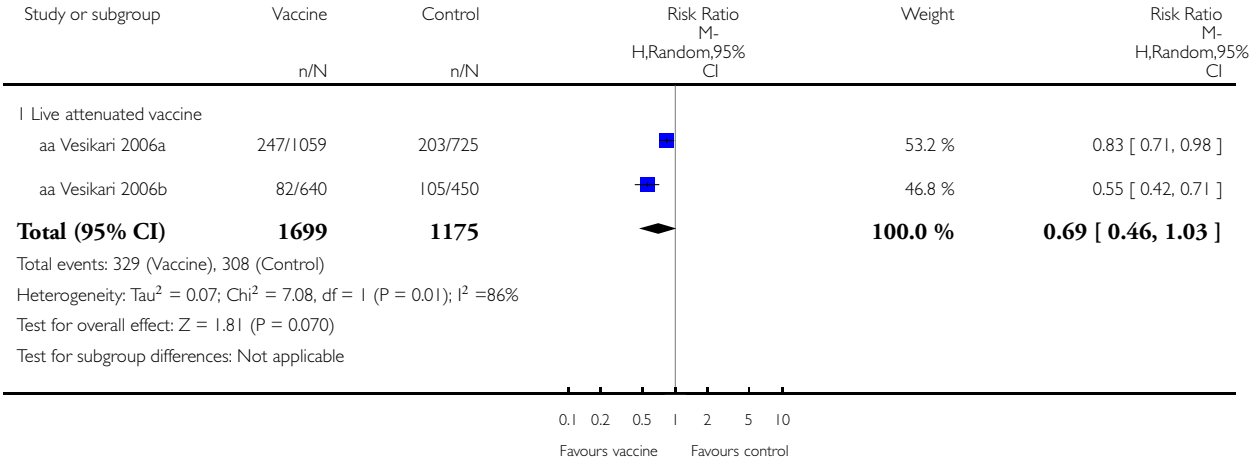
Analysis 8.10. Comparison 8 Vaccine versus placebo, Outcome 10 Working days lost (number of events, parents of children 6-36 months of age).

Review: Vaccines for preventing influenza in healthy children

Comparison: 8 Vaccine versus placebo

Outcome: 10 Working days lost (number of events, parents of children 6-36 months of age)



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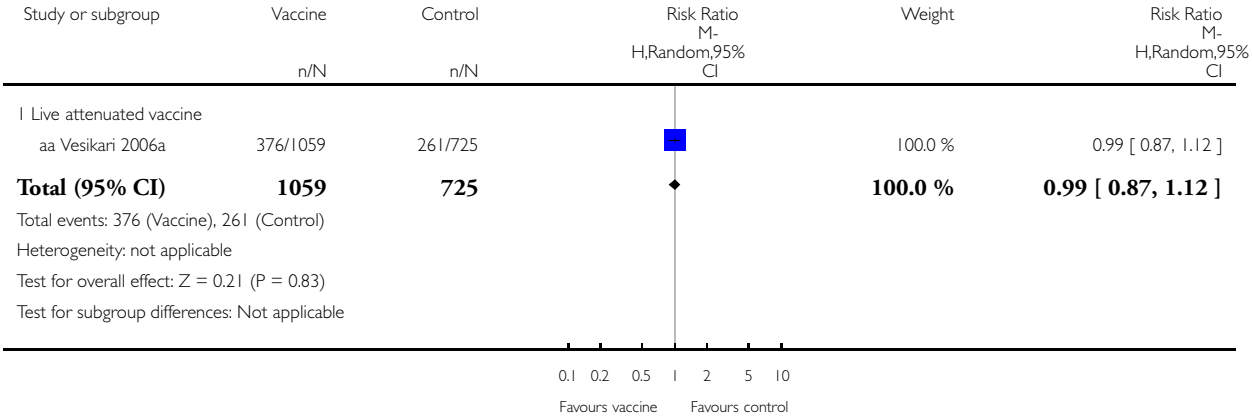
Analysis 8.11. Comparison 8 Vaccine versus placebo, Outcome 11 Drug prescriptions (number of events, 6-36 months of age).

Review: Vaccines for preventing influenza in healthy children

Comparison: 8 Vaccine versus placebo

Outcome: 11 Drug prescriptions (number of events, 6-36 months of age)



ADDITIONAL TABLES

Table 1. Sensitivity analysis

Comparison	Vaccine type	Study type	Outcome	Age group	Without Russian studies	Datasets	All studies	Datasets
					Risk ratio (random) (95% CI)		Risk ratio (random) (95% CI)	
01.01	Live	RCTs	Influenza	</= 2 years				
				</= 6 years	0.15 (0.10 to 0.23)	5	0.15 (0.10 to 0.23)	5
				> 6 years	0.47 (0.23 to 0.97)	1	0.47 (0.23 to 0.97)	1
				Total	0.18 (0.11 to 0.29)	6	0.18 (0.11 to 0.29)	6

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Table 1. Sensitivity analysis (*Continued*)

01.02	Live	RCTs	ILI	</= 2 years				
				</= 6 years	0.54 (0.12 to 2.42)*	1	0.67 (0.57 to 0.77)	5
				> 6 years	0.12 (0.01 to 2.11)*	1	0.67 (0.60 to 0.74)	8
				Total	0.39 (0.10 to 1.48)*	2	0.67 (0.62 to 0.72)	13
02.01	Inactivated	RCTs	Influenza	</= 2 years	0.55 (0.18 to 1.69)	2	0.55 (0.18 to 1.69)	2
				</= 6 years	0.61 (0.34 to 1.08)	2	0.61 (0.34 to 1.08)	2
				> 6 years	0.31 (0.22 to 0.45)	3	0.31 (0.22 to 0.45)	3
				Total	0.41 (0.29 to 0.59)	7	0.41 (0.29 to 0.59)	7
02.02	Inactivated	RCTs	ILI	</= 2 years				
				</= 6 years	0.39 (0.21 to 0.69)	3	0.39 (0.21 to 0.69)	3
				> 6 years	0.24 (0.08 to 0.70)+	2	0.72 (0.66 to 0.78)	4
				Total	0.34 (0.24 to 0.50)+	5	0.64 (0.54 to 0.76)	7
03.01	Live	Cohort studies	Influenza	</= 2 years				
				</= 6 years				
				> 6 years			0.56 (0.35 to 0.91)	1

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Table 1. Sensitivity analysis (*Continued*)

				Total	No studies		0.56 (0.35 to 0.91)	1
03.02	Live	Cohort studies	ILI	</= 2 years				
				</= 6 years				
				> 6 years	0.63 (0.57 to 0.69)	1	0.63 (0.57 to 0.69)	2
				Total	0.63 (0.57 to 0.69)	1	0.63 (0.57 to 0.69)	2
04.01	Inactivated	Cohort studies	Influenza	</= 2 years	0.63 (0.27 to 1.47)	3	0.63 (0.27 to 1.47)	3
				</= 6 years	0.34 (0.13 to 0.89)	1	0.34 (0.13 to 0.89)	1
				> 6 years	0.20 (0.10 to 0.39)*	1	0.36 (0.12 to 1.11)	2
				Total	0.36 (0.19 to 0.66)	5	0.42 (0.25 to 0.73)	6
04.02	Inactivated	Cohort studies	ILI	</= 2 years				
				</= 6 years	0.40 (0.13 to 1.20)	3	0.81 (0.65 to 1.01)	4
				> 6 years	0.10 (0.05 to 0.21)+	1	0.44 (0.29 to 0.68)	7
				Total	0.26 (0.07 to 0.92)+	4	0.55 (0.42 to 0.70)	11

ILI: Influenza-like illness
RCTs: randomised controlled trials
*: significance change
+: possible decision-making significant change

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Table 2. Risk of bias sensitivity analysis

			All datasets					Excluding studies with high risk of bias							
Comparisons		Effect measure	Number of datasets	Effect estimate	LL 95% CI	UL 95% CI	Statistical significance	Number of datasets	Effect estimate*	LL 95% CI	UL 95% CI	Statistical significance	VE absolute change	Change effect measure direction	Change in statistical significance
Analysis 1.1	Influenza	Risk ratio	7	0.20	0.13	0.32	Sign	5	0.23	0.12	0.49	Sign	-3%	Unchanged	Unchanged
Analysis 1.1.1	Under 2 years	Risk ratio	0	0	0	0	--	0	0	0	0	--		Unchanged	Unchanged
Analysis 1.1.2	Under 6 years	Risk ratio	6	0.18	0.11	0.29	Sign	4	0.20	0.10	0.42	Sign	-2%	Unchanged	Unchanged
Analysis 1.1.3	Over 6 years	Risk ratio	1	0.47	0.23	0.97	Sign	1	0.47	0.23	0.97	Sign	0%	Unchanged	Unchanged
Analysis 1.2	Influenza-like illness	Risk ratio	13	0.67	0.62	0.72	Sign	5	0.5	0.45	0.55	Sign	17%	Unchanged	Unchanged
Analysis 1.2.1	Under 2 years	Risk ratio	0	0	0	0	--	0	0	0	0	--		Unchanged	Unchanged
Analysis 1.2.2	Under 6 years	Risk ratio	5	0.67	0.57	0.77	Sign	2	0.48	0.44	0.54	Sign	19%	Unchanged	Unchanged
Analysis 1.2.3	Over 6 years	Risk ratio	8	0.67	0.6	0.74	Sign	3	0.55	0.4	0.76	Sign	12%	Unchanged	Unchanged
Analysis 2.1	Influenza	Risk ratio	7	0.41	0.29	0.59	Sign	7	0.41	0.29	0.59	Sign	0%	Unchanged	Unchanged

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Table 2. Risk of bias sensitivity analysis (*Continued*)

Analysis 2.1.1	Under 2 years	Risk ratio	2	0.55	0.18	1.69	No sign	2	0.55	0.18	1.69	No sign	0%	Unchanged	Unchanged
Analysis 2.1.2	Under 6 years	Risk ratio	2	0.61	0.34	1.08	No Sign	2	0.61	0.34	1.08	No Sign	0%	Unchanged	Unchanged
Analysis 2.1.3	Over 6 years	Risk ratio	3	0.31	0.22	0.45	Sign	3	0.31	0.22	0.45	Sign	0%	Unchanged	Unchanged
Analysis 2.2	Influenza-like illness	Risk ratio	7	0.64	0.54	0.76	Sign	4	0.39	0.19	0.8	Sign	25%	Unchanged	Unchanged
Analysis 2.2.1	Under 2 years	Risk ratio	0	0	0	0	--	0	0	0	0	--		Unchanged	Unchanged
Analysis 2.2.2	Under 6 years	Risk ratio	3	0.39	0.21	0.69	Sign	2	0.52	0.14	1.98	No sign	-13%	Unchanged	Changed
Analysis 2.2.3	Over 6 years	Risk ratio	4	0.72	0.66	0.78	Sign	2	0.24	0.08	0.7	Sign	48%	Unchanged	Unchanged
Analysis 3.1	Influenza	Risk ratio	1	0.56	0.35	0.91	Sign	0	0	0	0	--		Unchanged	Changed
Analysis 3.1.1	Under 2 years	Risk ratio	0	0	0	0	--	0	0	0	0	--		Unchanged	Unchanged
Analysis 3.1.2	Under 6 years	Risk ratio	0	0	0	0	--	0	0	0	0	--		Unchanged	Unchanged
Analysis 3.1.3	Over 6 years	Risk ratio	1	0.56	0.35	0.91	Sign	0	0	0	0	--		Unchanged	Changed
Analysis 3.2	Influenza-like	Risk ratio	2	0.63	0.57	0.69	Sign	0	0	0	0	--		Unchanged	Changed

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Table 2. Risk of bias sensitivity analysis (*Continued*)

	illness														
Analysis 3.2.1	Under 2 years	Risk ratio	0	0	0	0	--	0	0	0	0	--		Unchanged	Unchanged
Analysis 3.2.2	Under 6 years	Risk ratio	0	0	0	0	--	0	0	0	0	--		Unchanged	Unchanged
Analysis 3.2.3	Over 6 years	Risk ratio	2	0.63	0.57	0.69	Sign	0	0	0	0	--		Unchanged	Changed
Analysis 4.1	Influenza	Risk ratio	6	0.42	0.25	0.73	Sign	0	0	0	0	--		Unchanged	Changed
Analysis 4.1.1	Under 2 years	Risk ratio	3	0.63	0.27	1.47	No sign	0	0	0	0	--		Unchanged	Changed
Analysis 4.1.2	Under 6 years	Risk ratio	1	0.34	0.13	0.89	Sign	0	0	0	0	--		Unchanged	Changed
Analysis 4.1.3	Over 6 years	Risk ratio	2	0.36	0.12	1.11	No sign	0	0	0	0	--		Unchanged	Changed
Analysis 4.2	Influenza-like illness	Risk ratio	13	0.53	0.42	0.67	Sign	0	0	0	0	--		Unchanged	Changed
Analysis 4.2.1	Under 2 years	Risk ratio	1	0.47	0.23	0.93	Sign	0	0	0	0	--		Unchanged	Changed
Analysis 4.2.2	Under 6 years	Risk ratio	5	0.74	0.59	0.93	Sign	1	0.98	0.94	1.03	No sign	-24%	Unchanged	Changed
Analysis 4.2.3	Over 6 years	Risk ratio	7	0.44	0.29	0.68	Sign	0	0	0	0	--		Unchanged	Changed

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Table 2. Risk of bias sensitivity analysis (*Continued*)

Analysis 4.3	Otitis media	Risk ratio	1	0.48	0.22	1.03	No sign	0	0	0	0	--		Unchanged	Changed
Analysis 4.3.1	Children aged 6 months to 5 years	Risk ratio	1	0.48	0.22	1.03	No sign	0	0	0	0	--		Unchanged	Changed
Analysis 5.1	Influenza	Risk ratio	7	0.19	0.11	0.32	Sign	5	0.21	0.09	0.48	Sign	-2%	Unchanged	Unchanged
Analysis 5.1.1	Live attenuated vaccines (1 dose)	Risk ratio	5	0.23	0.12	0.47	Sign	3	0.38	0.2	0.75	Sign	-11%	Unchanged	Unchanged
Analysis 5.1.2	Live attenuated vaccines (2 doses)	Risk ratio	2	0.11	0.04	0.26	Sign	2	0.11	0.04	0.26	Sign	0%	Unchanged	Unchanged
Analysis 5.2	Influenza-like illness	Risk ratio	8	0.69	0.6	0.8	Sign	3	0.53	0.39	0.74	Sign	16%	Unchanged	Unchanged
Analysis 5.2.1	Live attenuated vaccines (1 dose)	Risk ratio	2	0.64	0.18	2.22	No sign	1	0.27	0.06	1.16	No sign	37%	Unchanged	Unchanged
Analysis 5.2.2	Live attenuated vac-	Risk ratio	6	0.66	0.57	0.76	Sign	2	0.55	0.39	0.79	Sign	11%	Unchanged	Unchanged

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Table 2. Risk of bias sensitivity analysis (*Continued*)

	cines (2 doses)														
Analysis 5.3	Otitis media (all episode	Risk ratio	2	0.98	0.95	1.01	No sign	1	0.98	0.95	1.01	No sign	0%	Unchanged	Unchanged
Analysis 5.4	Working days lost (number of events, parents)	Risk ratio	2	0.69	0.46	1.03	No sign	2	0.69	0.46	1.03	No sign	0%	Unchanged	Unchanged
Analysis 5.5	Drug prescriptions (number of events)	Risk ratio	1	0.99	0.87	1.12	No sign	1	0.99	0.87	1.12	No sign	0%	Unchanged	Unchanged
Analysis 5.6	Outpatients attendance for pneumonia and influenza	Risk ratio	2	0.76	0.59	0.98	Sign	2	0.76	0.59	0.98	Sign	0%	Unchanged	Unchanged
Analysis 6.1	Influenza	Risk ratio	5	0.36	0.28	0.48	Sign	5	0.36	0.28	0.48	Sign	0%	Unchanged	Unchanged
Analysis 6.1.1	Inactivated vac-	Risk ratio	5	0.36	0.28	0.48	Sign	5	0.36	0.28	0.48	Sign	0%	Unchanged	Unchanged

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Table 2. Risk of bias sensitivity analysis (*Continued*)

	cines (1 dose)														
Analysis 6.1.2	Inactivated vaccines (2 doses)	Risk ratio	0	0	0	0	--	0	0	0	0	--		Unchanged	Unchanged
Analysis 6.2	Influenza-like illness	Risk ratio	4	0.72	0.65	0.79	Sign	2	0.35	0.15	0.81	Sign	37%	Unchanged	Unchanged
Analysis 6.2.1	Inactivated vaccines (1 dose)	Risk ratio	2	0.35	0.15	0.81	Sign	2	0.35	0.15	0.81	Sign	0%	Unchanged	Unchanged
Analysis 6.2.2	Inactivated vaccines (2 doses)	Risk ratio	2	0.72	0.69	0.76	Sign	0	0	0	0	--		Unchanged	Unchanged
Analysis 7.1	Influenza vs ILI (crude data)	Odds Ratio					--					--		Unchanged	Unchanged
Analysis 7.1.1	Children aged below 6 years	Odds Ratio	9	0.59	0.45	0.77	Sign	6	0.55	0.44	0.7	Sign	4%	Unchanged	Unchanged
Analysis 7.1.2	Children aged	Odds Ratio	1	0.76	0.07	8.66	No sign	1	0.76	0.07	8.66	No sign	0%	Unchanged	Unchanged

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Table 2. Risk of bias sensitivity analysis (*Continued*)

	5 to 19 years														
Analysis 7.2	Influenza vs ILI (adj. estimates)	Odds Ratio					--					--		Unchanged	Unchanged
Analysis 7.2.1	Children aged below 23 months to fully vaccinated	Odds Ratio	7	0.6	0.39	0.94	Sign	4	0.46	0.29	0.73	Sign	14%	Unchanged	Unchanged
Analysis 7.2.2	Children aged 24 to 59 months to fully vaccinated	Odds Ratio	4	0.4	0.22	0.7	Sign	4	0.4	0.22	0.7	Sign	0%	Unchanged	Unchanged
Analysis 7.2.3	Children aged 6 to 59 months to fully vaccinated	Odds Ratio	5	0.45	0.32	0.62	Sign	5	0.45	0.32	0.62	Sign	0%	Unchanged	Unchanged
Analysis 7.2.4	Children aged below 14 years	Odds Ratio	1	0.23	0.06	0.84	Sign	1	0.23	0.06	0.84	Sign	0%	Unchanged	Unchanged

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Table 2. Risk of bias sensitivity analysis (*Continued*)

	old to fully vaccinated													
Analysis 7.3	Influenza-like illness vs no symptoms	Odds Ratio	2	0.49	0.28	0.86	Sign	0	0	0	0	--		Unchanged	Changed
Analysis 7.3.1	Inactivated vaccine (1 dose)	Odds Ratio	1	0.53	0.26	1.07	No sign	0	0	0	0	--		Unchanged	Changed
Analysis 7.3.2	Inactivated vaccine (2 doses)	Odds Ratio	1	0.44	0.18	1.1	No sign	0	0	0	0	--		Unchanged	Changed
Analysis 8.1	Influenza	Risk ratio	11	0.27	0.18	0.42	Sign	11	0.27	0.18	0.42	Sign	0%	Unchanged	Unchanged
Analysis 8.1.1	Live attenuated vaccines (1 dose)	Risk ratio	4	0.27	0.12	0.61	Sign	4	0.27	0.12	0.61	Sign	0%	Unchanged	Unchanged
Analysis 8.1.2	Live attenuated vaccines (2 doses)	Risk ratio	2	0.11	0.04	0.26	Sign	2	0.11	0.04	0.26	Sign	0%	Unchanged	Unchanged

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Table 2. Risk of bias sensitivity analysis (*Continued*)

Analysis 8.1.3	Inactivated vaccines (1 dose)	Risk ratio	5	0.36	0.28	0.48	Sign	5	0.36	0.28	0.48	Sign	0%	Unchanged	Unchanged
Analysis 8.1.4	Inactivated vaccines (2 doses)	Risk ratio	0	0	0	0	--	0	0	0	0	--		Unchanged	Unchanged
Analysis 8.2	Influenza-like illness	Risk ratio	12	0.69	0.62	0.77	Sign	5	0.5	0.38	0.67	Sign	19%	Unchanged	Unchanged
Analysis 8.2.1	Live attenuated vaccines (1 dose)	Risk ratio	2	0.64	0.18	2.22	No sign	1	0.27	0.06	1.16	No sign	37%	Unchanged	Unchanged
Analysis 8.2.2	Live attenuated vaccines (2 doses)	Risk ratio	6	0.66	0.57	0.76	Sign	2	0.55	0.39	0.79	Sign	11%	Unchanged	Unchanged
Analysis 8.2.3	Inactivated vaccines (1 dose)	Risk ratio	2	0.35	0.15	0.81	Sign	2	0.35	0.15	0.81	Sign	0%	Unchanged	Unchanged
Analysis 8.2.4	Inactivated vac-	Risk ratio	2	0.72	0.69	0.76	Sign	0	0	0	0	--		Unchanged	Changed

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Table 2. Risk of bias sensitivity analysis (*Continued*)

	cines (2 doses)														
Analysis 8.3	Secondary cases	Risk ratio	1	1.68	0.56	4.99	No sign	1	1.68	0.56	4.99	No sign	0%	Unchanged	Unchanged
Analysis 8.3.1	Live attenuated vaccines (1 dose)	Risk ratio	0	0	0	0	--	0	0	0	0	--		Unchanged	Unchanged
Analysis 8.3.2	Live attenuated vaccines (2 doses)	Risk ratio	0	0	0	0	--	0	0	0	0	--		Unchanged	Unchanged
Analysis 8.3.3	Inactivated vaccines (1 dose)	Risk ratio	1	1.68	0.56	4.99	No sign	1	1.68	0.56	4.99	No sign	0%	Unchanged	Unchanged
Analysis 8.3.4	Inactivated vaccines (2 doses)	Risk ratio	0	0	0	0	--	0	0	0	0	--		Unchanged	Unchanged
Analysis 8.4	School absenteeism	Risk ratio	2	0.49	0.26	0.92	Sign	2	0.49	0.26	0.92	Sign	0%	Unchanged	Unchanged
Analysis 8.4.1	Live attenuated vac-	Risk ratio	1	0.51	0.22	1.19	No sign	1	0.51	0.22	1.19	No sign	0%	Unchanged	Unchanged

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Table 2. Risk of bias sensitivity analysis (*Continued*)

	cines (1 dose)														
Analysis 8.4.2	Live attenuated vaccines (2 doses)	Risk ratio	0	0	0	0	--	0	0	0	0	--		Unchanged	Unchanged
Analysis 8.4.3	Inactivated vaccines (1 dose)	Risk ratio	1	0.46	0.17	1.22	No sign	1	0.46	0.17	1.22	No sign	0%	Unchanged	Unchanged
Analysis 8.4.4	Inactivated vaccines (2 doses)	Risk ratio	0	0	0	0	--	0	0	0	0	--		Unchanged	Unchanged
Analysis 8.5	Lower respiratory tract disease	Risk ratio	3	0.2	0.03	1.54	No sign	2	0.52	0.08	3.37	No sign	-32%	Unchanged	Unchanged
Analysis 8.5.1	Live attenuated vaccines (1 dose)	Risk ratio	2	0.16	0.01	4.45	No sign	1	0.73	0.07	7.88	No sign	-57%	Unchanged	Unchanged
Analysis 8.5.2	Live attenuated vaccines	Risk ratio	0	0	0	0	--	0	0	0	0	--		Unchanged	Unchanged

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Table 2. Risk of bias sensitivity analysis (*Continued*)

	(2 doses)														
Analysis 8.5.3	Inactivated vaccines (1 dose)	Risk ratio	1	0.3	0.01	6.17	No sign	1	0.3	0.01	6.17	No sign	0%	Unchanged	Unchanged
Analysis 8.5.4	Inactivated vaccines (2 doses)	Risk ratio	0	0	0	0	--	0	0	0	0	--		Unchanged	Unchanged
Analysis 8.6	Acute otitis media	Risk ratio	7	1	0.79	1.26	No sign	5	1.03	0.91	1.17	No sign	-3%	Unchanged	Unchanged
Analysis 8.6.1	Live attenuated vaccines (1 dose)	Risk ratio	3	0.42	0.05	3.79	No sign	1	1.46	0.09	22.93	No sign	-104%	Unchanged	Unchanged
Analysis 8.6.2	Live attenuated vaccines (2 doses)	Risk ratio	1	0.98	0.95	1.01	No sign	1	0.98	0.95	1.01	No sign	0%	Unchanged	Unchanged
Analysis 8.6.3	Inactivated vaccines (1 dose)	Risk ratio	1	1.52	0.1	23.76	No sign	1	1.52	0.1	23.76	No sign	0%	Unchanged	Unchanged

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Table 2. Risk of bias sensitivity analysis (*Continued*)

Analysis 8.6.4	Inactivated vaccines (2 doses)	Risk ratio	2	1.15	0.95	1.4	No sign	2	1.15	0.95	1.4	No sign	0%	Unchanged Unchanged
Analysis 8.7	Hospitalisation due to acute otitis media	Risk ratio					--					--		Unchanged Unchanged
Analysis 8.7.1	Inactivated vaccine (2 doses)	Risk ratio	2	1.41	0.62	3.24	No sign	2	1.41	0.62	3.24	No sign	0%	Unchanged Unchanged
Analysis 8.8	Consequences of acute otitis media	Mean Difference					--					--		Unchanged Unchanged
Analysis 8.8.1	Inactivated vaccine, 2 doses visits	Mean Difference	2	-0.02	-0.27	0.23	No sign	2	-0.02	-0.27	0.23	No sign		Unchanged Unchanged
Analysis 8.8.2	Inactivated vaccine	Mean Difference	2	0.13	-0.36	0.63	No sign	2	0.13	-0.36	0.63	No sign		Unchanged Unchanged

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Table 2. Risk of bias sensitivity analysis (*Continued*)

	(2 doses; courses of antibiotics														
Analysis 8.9	Outpatients attendance for pneumonia and influenza	Risk ratio	2	0.76	0.59	0.98	Sign	1	0.85	0.75	0.96	Sign	-9%	Unchanged	Unchanged
Analysis 8.9.1	Live attenuated vaccine (1 dose)	Risk ratio	1	0.65	0.49	0.85	Sign	0	0	0	0	--		Unchanged	Changed
Analysis 8.9.2	Live attenuated vaccine (2 doses)	Risk ratio	1	0.85	0.75	0.96	Sign	1	0.85	0.75	0.96	Sign	0%	Unchanged	Unchanged
Analysis 8.10	Working days lost (number of events, parents of children	Risk ratio	2	0.69	0.46	1.03	No sign	1	0.83	0.71	0.98	Sign	-14%	Unchanged	Changed

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Table 2. Risk of bias sensitivity analysis (*Continued*)

	6 to 36 months of age)														
Analysis 8.10.1	Live attenuated vaccine	Risk ratio	2	0.69	0.46	1.03	No sign	1	0.83	0.71	0.98	Sign	-14%	Unchanged	Changed
Analysis 8.11	Drug prescriptions (number of events, 6 to 36 months of age)	Risk ratio	1	0.99	0.87	1.12	No sign	1	0.99	0.87	1.12	No sign	0%	Unchanged	Unchanged
Analysis 8.11.1	Live attenuated vaccine	Risk ratio	1	0.99	0.87	1.12	No sign	1	0.99	0.87	1.12	No sign	0%	Unchanged	Unchanged

CI: confidence interval
LL: lower limit
No sign: when effect measure is not statistically significant
risk ratio*: effect estimate excluding high risk of bias datasets
Sign: when effect measure is statistically significant
UL: upper limit
VE absolute change = (1-RR*)-(1-RR)

Table 3. Efficacy and effectiveness data from intraepidemic and non-typical studies

Study reference	Exclusion reason	RCT/ Cohort	Vaccine	Age group	Outcome	n treatment	N treatment	n control	N control
Nicholls 2004	Cohort from community not repre-	Cohort	Inactive, trivalent	0 to 2 years	ILI	11	18	3	5

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Table 3. Efficacy and effectiveness data from intraepidemic and non-typical studies (*Continued*)

	sentative of local population								
Nicholls 2004	Cohort from community not representative of local population	Cohort	Inactive, trivalent	3 to 4 years	ILI	10	16	0	0
Nicholls 2004	Cohort from community not representative of local population	Cohort	Inactive, trivalent	5 to 14 years	ILI	39	91	0	3
Slepushkin 1974	Intraepidemic study of orally administered vaccine as emergency prophylaxis	RCT	Live (oral) H2N2+B	1 to 3 years	Influenza or ARI >= 10 days after vaccination	187	508	271	492
Ritzwoller 2005	Intraepidemic study	Cohort	Inactive, trivalent	6 to 23 months	ILI	65	1129	124	1615
Aksenov 1971	Intraepidemic study	Cohort	Live, H2N2 +B, 3 doses 5 days apart	4 to 7 years	Morbidity due to influenza and ARI	107	760	164	594
Aksenov 1971	Intraepidemic study	Cohort	Live, H2N2 +B, 3 doses 8 to 10 days apart	4 to 7 years	Morbidity due to influenza and ARI	81	728	193	674

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Table 3. Efficacy and effectiveness data from intraepidemic and non-typical studies (*Continued*)

Aksenov 1971	Intraepidemic study	Cohort	Live, H2N2 +B, 3 doses 5 days apart	7 to 15 years	Morbidity due to influenza and ARI	143	1358	114	776

ARI: acute respiratory infection
ILI: influenza-like illness

APPENDICES

Appendix 1. Included study designs

A case-control study is a prospective or retrospective epidemiological study usually used to investigate the causes of disease. Study participants who have experienced an adverse outcome or disease are compared with participants who have not. Any differences in the presence or absence of hypothesised risk factors are noted.

A cohort study is an epidemiological study where groups of individuals are identified who vary in their exposure to an intervention or hazard and are then followed to assess outcomes. Association between exposure and outcome are then estimated. Cohort studies are best performed prospectively but can also be undertaken retrospectively if suitable data records are available.

A randomised controlled trial (RCT) is any study on humans in which the individuals (or other experimental units) followed in the study were definitely or possibly assigned prospectively to one of two (or more) alternative forms of health care using random allocation.

A quasi-randomised clinical trial (SRCT) is any study on humans in which the individuals (or other experimental units) followed in the study were definitely or possibly assigned prospectively to one of two (or more) alternative forms of health care using some quasi-random method of allocation (such as alternation, date of birth, or case record number).

Appendix 2. Previous search strategy

For this review update, we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2007, Issue 3); OLD MEDLINE (1950 to 1965); MEDLINE (1969 to September 2007); EMBASE (1974 to September 2007); Biological Abstracts (1969 to September 2007); and Science Citation Index (1974 to September 2007).

We used the following search terms to search MEDLINE and CENTRAL and adapted them for the other electronic databases.

MEDLINE (OVID)

1 exp Influenza Vaccine
2 exp INFLUENZA/
3 exp VACCINES/
4 and/2-3
5 ((influenza or flu) adj (vaccin$ or immuni$ or innoculat$))
6 1 or 4 or 5
7 limit 6 to all child <0 to 18 years>
8 exp CHILD/
9 (child or children or pediatric or paediatric)
10 or/8-9
11 6 and 10
12 7 or 11

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13 RANDOMIZED CONTROLLED TRIAL
14 CONTROLLED CLINICAL TRIAL
15 RANDOMIZED CONTROLLED TRIALS
16 RANDOM ALLOCATION
17 DOUBLE BLIND METHOD
18 SINGLE-BLIND METHOD
19 or/13-18
20 Animals/
21 human
22 20 not 21
23 19 not 22
24 CLINICAL TRIAL
25 exp Clinical Trials/
26 (clin$ adj25 trial$)
27 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$))
28 PLACEBOS
29 placebo$
30 random$
31 or/24-30
32 31 not 22
33 exp Case-Control Studies/
34 case control stud$
35 (case$ and control$)
36 exp Cohort Studies/
37 cohort stud$
38 exp Cross-Over Studies/
39 cross over stud$
40 or/33-39
41 40 not 22
42 23 or 32 or 41
43 12 and 42

We imposed no language or publication restrictions. The search of CENTRAL included any trial reports identified in the systematic handsearch of the journal, *Vaccine*.

In order to identify additional published and unpublished studies we searched the Vaccine Adverse Event Reporting System Website (http://www.vaers.org). We contacted vaccine manufacturers and first or corresponding authors of relevant studies to identify further published or unpublished trials.

Appendix 3. CENTRAL 2011, Issue 3 search strategy

We used the following search terms to search CENTRAL (16 Nov 2011).

No.	----------Query----------
#1	MeSH descriptor Influenza Vaccines explode all trees
#2	MeSH descriptor Influenza, Human explode all trees with qualifiers: CO,EP,IM,MO,PC,TM
#3	(influenza OR flu OR grippe) NEAR/5 (vaccin* OR immuni* OR inocul*) :ti,ab,kw
#4	(#1 OR #2 OR #3)

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(*Continued*)

#5	(child* OR preschool* OR school* OR young OR adolescent* OR infant* OR toddler* OR pediatric* OR paediatric* OR infant*):ti,ab,kw
#6	(#4 AND #5)
#7	(#6)from 2007 to 2011

Appendix 4. EMBASE search strategy

We used the following search terms to search EMBASE (16 Nov 2011).

No.	Query
#1	'influenza vaccine'/exp OR 'influenza vaccine' OR (influenza OR flu AND (vaccin* OR immuni* OR inoculat*)) OR 'influenza vaccine'/syn OR ('influenza'/exp AND 'vaccine'/exp)
#2	'case control study'/syn OR 'case control':de,ab,ti OR (cases:ab,ti AND controls:ab,ti) OR 'cohort analysis'/syn OR 'cohort study':de,ab,ti OR 'study cohort':de,ab,ti OR prospectiv*:ab,ti OR volunteer*:ab,ti OR observational:ab,ti OR 'clinical trial':it OR 'randomized controlled trial':it OR 'drug therapy'/exp OR 'drug therapy':de OR randomized:ab,ti OR randomised:ab,ti OR placebo:ab,ti OR randomly:ab,ti OR trial:ab,ti OR groups:ab,ti
#3	'clinical trial':it OR 'randomized controlled trial':it OR 'randomized controlled trial'/exp OR 'randomisation'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'clinical trial'/exp OR 'clinical' NEAR/0 'trial' OR 'clinical trial' OR (singl* OR doubl* OR trebl* OR tripl* AND (mask* OR blind*)) OR 'placebo'/exp OR placebo* OR random* OR 'control group'/exp OR 'experimental design'/exp OR 'comparative study'/exp OR 'evaluation study' OR 'evaluation studies'/exp OR 'follow up'/exp OR 'prospective study'/exp OR control* OR prospectiv* OR volunteer* AND [humans]/lim
#4	#2 OR #3
#5	#1 AND #4
#6	#5 AND ([newborn]/lim OR [infant]/lim OR [child]/lim OR [adolescent]/lim)
#7	child*:de,ab,ti OR preschool*:de,ab,ti OR school*:de,ab,ti OR young:de,ab,ti OR adolescent*:de,ab,ti OR toddler*:de,ab,ti OR pediatric*:de,ab,ti OR paediatric*:de,ab,ti OR infant*:de,ab,ti
#8	#5 AND #7
#9	#6 OR #8

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Appendix 5. Data extraction form

PART 1

Background information and description of study

Reviewer:

Study unique identifier:

Published: Y/N

Journal (if applicable):

Year of publication:

Period study conducted:

Abstract/Full paper:

Country or countries of study:

Number of studies included in this paper:

Funding source (delete non-applicable items):

Government, Pharmaceutical, Private, Unfunded, Unclear

Paper/abstract numbers of other studies with which these data are linked:

Reviewer's assessment of study design (delete non-applicable items):

Study category - study design

Experimental studies - RCT/CCT; historical controlled trial (HCT); cross-over (X-over) RCT

Non-randomised analytical studies (specifically designed to assess association) - prospective/retrospective cohort; case control; X-sectional

Non-randomised comparative studies (studies not specifically designed to assess association) - case X-over/time series; ecological study; indirect comparison (before and after)

Non-comparative studies - EXCLUDE

Does the study present data distributed by age group/occupation/health status? (Yes/No)

Subgroup distribution

Age group Y/N

Occupation Y/N

Health status Y/N

Immunisation status/schedule Y/N

Gender Y/N

Risk group Y/N

Description of study

Methods

Participants

Interventions/Exposure

Outcomes

Notes

Part 2a

Methodological Quality Assessment

RCT and CCT only

Randomisation:

A = individual participants allocated to vaccine or control group

B = groups of participants allocated to vaccine or control group

Generation of the allocation sequence:

A = adequate, for example table of random numbers or computer generated random numbers

B = inadequate, for example alternation, date of birth, day of the week or case record number

C = not described

Allocation concealment:

A = adequate, for example numbered or coded identical containers administered sequentially, on-site computer system that can only be accessed after entering the characteristics of an enrolled participant or serially numbered, opaque, sealed envelopes

B = possibly adequate, for example sealed envelopes that are not sequentially numbered or opaque

C = inadequate, for example open table of random numbers

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D = not described
Blinding:
A = adequate double-blinding, for example placebo vaccine
B = single-blind, i.e. blinded outcome assessment
C = no blinding
Follow up:
Average duration of follow-up and number of losses to follow-up

Part 2b

Description of interventions and outcomes
RCT and CCT only
Vaccines used
Vaccine and composition | Product and manufacturer | Schedule & dosage and status | Route of administration
Arm 1
Arm 2
Arm 3
Arm 4
Placebo
Rule: index vaccine goes in the Arm 1 line, placebo in the last line
Status: primary, secondary or tertiary immunisation
Vaccine batch numbers
Details of participants
Enrolled | Missing | Reasons | Inclusion in analysis | Notes
Active arm 1
Active arm 2
Active arm 3
Active arm 4
Controls
Outcomes List - Efficacy and Effectiveness
Outcome | How defined | Description/Follow-up/Notes
Outcomes List - Safety
Outcome | How defined | Description/Follow-up/Notes
Investigators to be contacted for more information? Yes/No
Contact details (principal investigator, fill in only if further contact is necessary):

Part 2c

Data Extraction and manipulation
(to be used for dichotomous or continuous outcomes)
RCT and CCT only
Comparison
Outcomes | n/N Index Arm | n/N Comparator
Outcomes | n/N Index Arm | n/N Comparator
Outcomes | n/N Index Arm | n/N Comparator
Outcomes | n/N Index Arm | n/N Comparator
Notes (for statistical use only)

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Appendix 6. Methodological quality of non-randomised studies

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE - CASE CONTROL STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Selection

1) Is the case definition adequate?

a) yes, with independent validation *

b) yes, e.g. record linkage or based on self-reports

c) no description

2) Representativeness of the cases

a) consecutive or obviously representative series of cases *

b) potential for selection biases or not stated

3) Selection of Controls

a) community controls *

b) hospital controls

c) no description

4) Definition of Controls

a) no history of disease (endpoint) *

b) no description of source

Comparability

1) Comparability of cases and controls on the basis of the design or analysis

a) study controls for ..... (Select the most important factor)*

b) study controls for any additional factor * (This criteria could be modified to indicate specific control for a second important factor)

Exposure

1) Ascertainment of exposure

a) secure record (e.g. surgical records) *

b) structured interview where blind to case/control status *

c) interview not blinded to case/control status

d) written self-report or medical record only

e) no description

2) Same method of ascertainment for cases and controls

a) yes *

b) no

3) Non-response rate

a) same rate for both groups *

b) non-respondents described

c) rate different and no designation

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE - COHORT STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for comparability

Selection

1) Representativeness of the exposed cohort

a) truly representative of the average ..... (describe) in the community*

b) somewhat representative of the average ..... in the community*

c) selected group of users e.g. nurses, volunteers

d) no description of the derivation of the cohort

2) Selection of the non-exposed cohort

a) drawn from the same community as the exposed cohort*

b) drawn from a different source

c) no description of the derivation of the non-exposed cohort

3) Ascertainment of exposure

a) secure record (e.g. surgical records) *

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b) structured interview *
c) written self-report
d) no description
4) Demonstration that outcome of interest was not present at start of study
a) yes *
b) no
Comparability
1) Comparability of cohorts on the basis of the design or analysis
a) study controls for ····· (select the most important factor) *
b) study controls for any additional factor * (This criteria could be modified to indicate specific control for a second important factor)
Outcome
1) Assessment of outcome
a) independent blind assessment *
b) record linkage *
c) self-report
d) no description
2) Was follow-up long enough for outcomes to occur
a) yes (select an adequate follow up period for outcome of interest) *
b) no
3) Adequacy of follow-up of cohorts
a) complete follow-up - all subjects accounted for *
b) subjects lost to follow-up unlikely to introduce bias - small number lost - > ···· % (select an adequate %) follow-up, or description provided of those lost) *
c) follow-up rate < ····% (select an adequate %) and no description of those lost
d) no statement

F E E D B A C K

Vaccines for preventing influenza in healthy children, 7 June 2012

Summary

The Cochrane article makes the claim that "*Inactivated vaccines have a lower efficacy (65%) than live attenuated vaccines and in children aged two or less, they appear to have similar effects to placebo, although this observation is based on a single small study (Hoberman 2003a).*" This conclusion regarding children under 2 years old seems to be erroneous, as the single study on which the result is based actually showed effectiveness in this age range against influenza infection in epidemic seasons. The reviewers may have been confused, as the paper by Hoberman et al does have lines like "*Given that our study did not find a significant difference between vaccine and placebo*," but this is regarding the primary objective of the study, which is (as is suggested by the study's title) to investigate the effectiveness of inactivated influenza vaccine in preventing Acute Otitis Media in young children. Note that while they may not have demonstrated a reduction in AOM, this does not mean that the vaccine was ineffective in preventing influenza infection.
The first cohort was during an epidemic season, and showed, "*efficacy rates against influenza in children aged 6 to 12 months, 13 to 18 months, and 19 to 24 months were 63%, 66%, and 69%, respectively.*" The second season failed to show an effect, but there were only 13 cases on influenza recorded for the second cohort, and influenza was infrequent, making it hard to come to any conclusion regarding effectiveness during that season.
I hope that this may prompt a revision of the claim that the vaccine was ineffective in the children under 2 years old, as the evidence in fact showed a rather substantial protective effect during the cohort exposed to epidemic influenza, and the seroprotection levels recorded in the study suggest that it should have performed similarly in the second cohort, had their been sufficient circulating influenza to detect a difference.
I agree with the conflict of interest statement below:

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I certify that I have no affiliations with or involvement in any organization or entity with a financial interest in the subject matter of my feedback.

Reply

Thank you. We have re-examined the evidence commented on by the reader. As the reader remarks, the primary objective of the trial by Hoberman et al was to assess the effects of TIV on otitis media (OM) in under two year olds. The secondary objectives "*were to evaluate the vaccine's safety, immunogenicity and efficacy against culture-proven influenza.....as well as...on children's utilisation of selected health care and related resources.*" (pdf page 2, just before "Methods"). See also our descriptive table of included studies.

Our comparison 2.1.1 shows the study's two influenza "seasons" (labelled as a and b). Overall the vaccine appears to have no effect. An equal lack of efficacy is seen against OM and resource utilisation.

Wide yearly differences in virus circulation as remarked on by the reader and observed by Hoberman and colleagues are precisely the reason why influenza vaccines studies should be carried out over several seasons and reviews of several studies are the most meaningful public health way to estimate the effects of influenza vaccines.

Hoberman A, Greenberg DP, Paradise JL, Rockette HE, Lave JR, Kearney DH, Colborn DK, Kurs-Lasky M, Haralam MA, Byers CJ, Zoffel LM, Fabian IA, Bernard BS, Kerr JD. Effectiveness of inactivated influenza vaccine in preventing acute otitis media in young children: a randomized controlled trial. JAMA 2003 Sep 24 ; 290 (12) : 1608 - 1616 .
Tom Jefferson and all co-authors.

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WHAT'S NEW

Last assessed as up-to-date: 16 November 2011.

Date	Event	Description
21 April 2017	Amended	Edits made to Abstract, Results and Discussion to correct a mistake with a decimal point and clarify the effects in children under two years of age

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HISTORY

Protocol first published: Issue 3, 2004

Review first published: Issue 1, 2006

Date	Event	Description
3 September 2014	Amended	Final sentence in paragraph three under 'Effects of interventions > Comparisons showing vaccines' efficacy' section has been amended. The value of NNV reported in the text (NNV = 28) was incorrect. It has been corrected to NNV = 2.8
21 June 2012	Feedback has been incorporated	Feedback comment and reply added to the review
16 November 2011	New search has been performed	For this 2011 update we included the following 15 new trials and datasets (aa Bracco Neto 2009a; aa Bracco Neto 2009b); (ba Cochran 2010a; ba Cochran 2010b; ba Cochran 2010c); (ba Eisenberg 2008a; ba Eisenberg 2008b); ba Gilca 2011; ba Kelly 2011; ba Kissling 2011; ba Mahmud 2011; ab Mallory 2010; ca Ortqvist 2011; ab Plennevaux 2011; (ba Staat 2011a; ba Staat 2011b); ba Valenciano 2011; ba Van Buynder 2010; ca Yin 2011; cb MPA 2011. Readers are reminded that one study may provide multiple datasets (i.e. Bracco Neto 2009 a and b) We excluded the following trials Ambrose 2011; Belshe 2008; Fujieda 2008; Haba-Rubio 2011; Jansen 2008; Kissling 2011a; McMahon 2008; Muhammad 2011; Stowe 2011; Wu 2010
16 November 2011	New citation required but conclusions have not changed	A new author joined the team to update this review
4 February 2008	New search has been performed	For the 2007 update we reran the searches and identified 1090 possible titles of interest. We retrieved 15 and excluded 5: Neuzil 2006, Hambidge 2006, France 2004 because they were non comparative, Daubeney 1997 because it had not been carried out in healthy children and Ghendon 2004 because it assessed the impact of vaccinating children to prevent influenza in the elderly. We included 10 studies. Two were placebo controlled trials of cold adapted live attenuated influenza vaccine (CAIV) (Tam 2007, Vesikari 2006), two (Anonymous 2005, Goodman 2006) were case-control studies assessing respectively the efficacy and safety of TIV, three were prospective cohort studies assessing the effectiveness of respectively CAIV (Wiggs-Stayner 2006), virosomal vaccine (Salleras 2006) and TIV vaccines (Fujieda 2006) and one was a retrospec-

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(*Continued*)

		tive cohort study (Allison 2006) assessing effectiveness of an undescribed vaccine. Two more studies included were a prospective cohort study reporting effectiveness and safety of CAIV in school-aged children (King 2006) and prospective single blind cohort study assessing effectiveness of TIV against OM (Ozgur 2006) . Our conclusions remain unchanged
15 January 2008	Amended	Converted to new review format.
10 November 2007	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Tom Jefferson (TOJ) co-wrote Background and Methods, Results and Discussion (efficacy and effectiveness) and interpreted the data.

Alessandro Rivetti (AR) conducted searches, co-ordinated retrieval of papers, identified papers for inclusion, extracted and checked data.

Eliana Ferroni (EF) applied inclusion criteria, co-extracted studies and wrote the paragraph on safety.

Carlo Di Pietrantonj (CDP) constructed comparisons for meta-analysis, checked data, identified papers for inclusion, analysed data, wrote statistical methods, co-wrote Results and interpreted the data.

Vittorio Demicheli (VD) co-wrote Background and Methods, determined papers for inclusion, arbitrated on quality assessment, constructed comparisons for meta-analysis and did a critical review of the existing review.

All authors contributed to and approved the revised text.

DECLARATIONS OF INTEREST

Tom Jefferson was an ad hoc consultant for F. Hoffman-La Roche Ltd in 1998 to 1999 on oseltamivir. He receives royalties from his books published by Blackwell and Il Pensiero Scientifico Editore, none of which are on neuraminidase inhibitors. He is occasionally interviewed by market research companies for anonymous interviews about Phase 1 or 2 products unrelated to influenza. He is acting as expert witness for the plaintiff in a legal case for claimed damages after exposure to a pandemic monovalent vaccine.

SOURCES OF SUPPORT

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Internal sources

- REGIONE PIEMONTE ASL 20 ALESSANDRIA, Italy.
for 2007 update, now ASL AL for 2012 update
- MRC Programme Grant G0000340, UK.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Case-Control Studies; Cohort Studies; Conflict of Interest; Influenza Vaccines [*therapeutic use]; Influenza, Human [*prevention & control]; Numbers Needed To Treat; Randomized Controlled Trials as Topic; Research Support as Topic; Vaccines, Attenuated [therapeutic use]; Vaccines, Inactivated [therapeutic use]

MeSH check words

Adolescent; Child; Child, Preschool; Humans; Infant

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