Vaccines for preventing influenza in healthy children (Review)

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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 old.

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) and document adverse events associated with influenza vaccines.

Search strategy

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2007, issue 3); OLD MEDLINE (1950 to 1965); MEDLINE (1966 to September 2007); EMBASE (1974 to September 2007); 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

Two review authors independently assessed trial quality and extracted data.

Main results

Fifty-one studies with 294,159 observations were included. Sixteen RCTs and 18 cohort studies were included in the analysis of vaccine efficacy and effectiveness. From RCTs, live vaccines showed an efficacy of 82% (95% confidence interval (CI) 71% to 89%) and an effectiveness of 33% (95% CI 28% to 38%) in children older than two compared with placebo or no intervention. Inactivated vaccines had a lower efficacy of 59% (95% CI 41% to 71%) than live vaccines but similar effectiveness: 36% (95% CI 24% to 46%). In children under two, the efficacy of inactivated vaccine was similar to placebo. 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 vaccines impeded meaningful analysis.

Authors' conclusions

Influenza vaccines are efficacious in children older than two but little evidence is available for children under two. There was a marked difference between vaccine efficacy and effectiveness. No safety comparisons could be carried out, emphasizing the need for standardisation of methods and presentation of vaccine safety data in future studies. 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 old in the USA and Canada. 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.

PLAIN LANGUAGE SUMMARY

Vaccines for preventing influenza in healthy children

Children and the elderly 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 respiratory tract, or both. Viruses are mainly of two subtypes (A or B) and spread periodically during the autumn-winter months.

Many other viruses however, can also cause illness of the respiratory tract.

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 month 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 (82% of illnesses were prevented) than injected vaccines made from the killed virus (59%). Neither type was particularly good at preventing 'flu-like illness' caused by other types of viruses (33% and 36% respectively). 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.

BACKGROUND

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 from time to time although the extent and severity of such epidemics varies widely. Efforts to prevent the yearly spread of influenza have had muted success but are essentially based on widespread vaccination.

Influenza vaccines currently available worldwide are of four types:

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 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 as a new vaccine 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 identification and isolation of viral strains circulating in the different parts of the world.

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 to 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 four years) (CDC 2007) and to healthy household contacts (including children) and caregivers of children aged below 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).

The main arguments for immunising young children (Izurieta 2000; Neuzil 2000; Principi 2004) and those attending school (Principi 2004; Reichert 2001) include: reduction of the number of patients with influenza; reduction in the number of admissions to hospital; mortality of the elderly in families with children; reduction in illness in health care workers; reduction in the number of antibiotic prescriptions and the reduction in absenteeism of children from school and their parents/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 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 (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 syncitial virus (RSV), mentioned above. 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 was 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

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 influenza-like illness 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, semi-randomised, cohort and case-controlled studies. For study design definitions see Appendix 1. It was 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. Studies which documented the inclusion of participants with chronic illnesses/conditions or immunodeficiency were excluded.

Types of interventions

Vaccination with any influenza vaccine given independently, in any dose, preparation or time schedule, compared with placebo, or with no intervention.
New as yet unlicensed types of vaccines were also considered (for example live attenuated and DNA vaccines).
Vaccination of staff in order to protect patients and residents admitted into hospitals, nursing homes, long-term care facilities were also, separately, considered.

Types of outcome measures

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 - symptoms of influenza only (measure of vaccine effectiveness).

3. Cases admitted to hospital.
4. Deaths of study participants (either from influenza or other causes).
5. Other direct or indirect indicator of disease impact not specified above.

Outcome measures for adverse events

1. Incidence of all types of local and systemic events recorded in clinical trials.
2. Frequency of all types of local and systemic events recorded in clinical trials.

Search methods for identification of studies

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).

The following search terms were used to search MEDLINE and CENTRAL and adapted 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$))
6 1 or 4 or 5
7 limit 6 to all child <0 to 18 years>
8 exp CHILD/
9 (child or children or pediatric or paediatric)
10 or/8-9
11 6 and 10
12 7 or 11
13 RANDOMIZED CONTROLLED TRIAL
14 CONTROLLED CLINICAL TRIAL
15 RANDOMIZED CONTROLLED TRIALS
16 RANDOM ALLOCATION
17 DOUBLE BLIND METHOD
18 SINGLE-BLIND METHOD
19 or/13-18
20 Animals/
21 human
22 20 not 21
23 19 not 22
24 CLINICAL TRIAL
25 exp Clinical Trials/
26 (clin$ 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

There were no language or publication restrictions. The search of CENTRAL included any trial reports identified in the systematic search by hand of the journal *Vaccine*.

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

Data collection and analysis

Inclusion procedure

Two review authors (SS, AR) independently excluded all studies not fulfilling inclusion criteria of initially identified and retrieved articles. Another review authors (TOJ) co-extracted the data for the 2007 update. CDP carried out statistical analyses.

Assessment of methodological quality

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 2005).

Studies were classified according to the following criteria:

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.
D = not described.
Blinding:
A = adequate double blinding, for example, placebo vaccine.
B = single blind, that is to say, blinded outcome assessment.
C = no blinding.
Follow up:
Average duration of follow up and number of losses to follow up.
Non-experimental studies:
Quality assessment of non-randomised studies were made in relation to the presence of potential confounders, which could make interpretation of the results difficult. The quality of case control (prospective and retrospective) and cohort studies was evaluated using the appropriate Newcastle-Ottawa Scales (NOS) (see Appendix 2).
Using quality at the analysis stage as a means of interpretation of the results, we assigned risk of bias categories on the basis of the number of items judged inadequate in each study: 1) low risk of bias: up to one inadequate item; 2) medium risk of bias: up to three inadequate items; and 3) high risk of bias: more than three inadequate items.

Arbitration procedure

In the case of disagreement in assigning quality criteria between the review authors (TOJ or SS and AR), arbitration was carried out by VD.

Data collection

Two review authors (SS , AR and TOJ and AR for the 2007 update) performed data extraction using a data extraction form (see Appendix 3). The data were checked and entered into Review Manager (RevMan) software. Data on the following were extracted:
- methodological quality of studies;
- study design (see Appendix 1);
- description of setting;
- characteristics of participants;
- description of vaccines (content and antigenic match);
- description of outcomes;
- publication status;
- date of study;
- location of study.

Data analysis

Data synthesis was carried out separately for live and inactivated vaccines. Studies were grouped for analysis according to study design - RCT, cohort studies, case-controlled study. For RCTs and cohort studies, sub-group analyses were carried out by age group as follows: under two years; under six years and over six years. The under two years group was selected as CDC recommends vaccination for healthy children aged 6 to 23 months (Harper 2004); the under six years and over six years categories reflected the most frequent stratification in primary studies.
Two comparisons (08 and 09), which included rare outcomes, included both vaccine types (live and inactivated). However, only the sub-group analyses were considered.
All comparisons made used numbers of participants completing trials.
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.
The relative risks of events was used for the comparisons of vaccine with placebo/control groups for RCTs and cohort studies; odds ratios were used for the single case-controlled study.
A sensitivity analysis was carried out which involved conducting the same comparisons but excluded studies from Russia.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.
Aksenov 1971
Aksenov 1971 was translated from Russian and describes a study of a live attenuated bivalent influenza A (H2N2) and B vaccine given as emergency prophylaxis during an epidemic in the USSR in 1969. The participants were 4890 children aged between 4 to 15 years. Treatments were randomly assigned to classes or alphabetically, so this has been classified as a cohort study. Children received three 0.5 ml doses of vaccine, the method of administration was unclear from the translated paper. Intervals between vaccine doses were reduced as vaccination took place at the beginning of an epidemic. School children received doses five to six days apart and for nursery school children, one group received their doses five days apart and another group 8 to 10 days apart. Doctors at schools and nurseries recorded any change in the condition of children and morbidity was recorded from 48 hours after vaccination to 6 to 10 days after completion of inoculations.
The outcomes assessed were morbidity due to influenza and an acute respiratory infection (ARI), pneumonia, bronchitis, tonsillitis, otitis media, serious and complicated influenza. Vaccine efficacy was evaluated based on total morbidity due to influenza

and ARIs. Children who did not receive all the vaccine doses or who had contracted influenza or ARI in 21 days before the first dose were excluded from the analysis. Serum samples taken from 35 children to determine epidemic strain - found to be A2/Hong Kong/1/68 (where A2 is H2N2).

The authors stated that there was a statistically reliable difference between the morbidity of the control group and the vaccinated group; severe and complicated influenza was recorded less often in vaccinated children. A difference in efficacy was observed between the vaccine administered with an 8 to 10 day interval and that administered with a 5 day interval. The authors conclude that the reduction in efficacy with a 5 day interval was due to a decrease in immunogenicity.

This study was not included in the analysis (intraepidermic study). Data are presented in Additional table 17.

Alexandrova 1986

Alexandrova 1986 is an RCT of live vaccine conducted in the former USSR from 1982 to 1983 on 29,955 pre-school (three to six years of age) and school aged (7 to 15 years of age) children. Participants were allocated to treatments in a stratified random manner by school; the vaccine was administered in 26 schools and 76 kindergartens and placebo in 19 schools and 66 kindergartens. Prior to conducting a full trial, reactogenicity tests were carried out on sub-groups of 267 children aged three to six years and 190 children aged 7 to 15, who were monitored for two days for fever. Two children were recorded with fever in the three to six year age group, both with temperatures under 37.5 ^{o}C compared with two in the placebo group, one of which had a temperature between 37.6 ^{o}C and 38.5 ^{o}C. In the 7 to 15 years age group, one child had a fever between 37.6 ^{o}C and 38.5 ^{o}C in the vaccinated group. The live attenuated vaccine tested was a mixture of recombinants 47/25/1 (H1N1) and 47/7/2 (H3N2). These were obtained from crosses of wild-type viruses A/Brazil/11/78 (H1N1) and A/Bangkok/1/79 (H3N2) with the cold-adapted donor strain A/Leningrad/134/47/57. The placebo administered was allantoic fluid from uninfected chicken embryos. The vaccines and placebo were administered intranasally in two doses of 0.25 ml, each given 28 to 30 days apart. The concentration of virus in the vaccine was 10^{7} EID_{50} /ml. Groups were evaluated in a double-blind fashion and the incidence of infectious and somatic disease in each child recorded in diaries. The incidence of influenza-like illness; pneumonia; otitis media; allergies; tonsillitis and pharyngitis; laryngitis and tracheitis (grouped together) were recorded for six months following the second inoculation. An outbreak of influenza was experienced in the region from 15 March to the end of April 1983 and the efficacy of the vaccines was measured only during this period. A definition of the epidemic was not given in the paper. The epidemic was caused by viruses A (H1N1) and A (H3N2) similar to A/Brazil/11/78 and A/Bangkok/1/79 and therefore similar to the recombinants included in the vaccine. The incidence of influenza and acute respiratory disease was recorded during the epidemic period, although no case definitions were given. This allowed an evaluation of vaccine effectiveness which was calculated by the authors as 2.06 for both age groups, that is to say the vaccine was 50% effective. There was statistically significant difference in incidence of influenza-like illness between the treatment group (22.9% of 3538 children) and the placebo group (43.6% of 3271 children). While the incidences of other disease outcomes were marginally higher in the placebo group, they are described by the authors as having a very similar distribution to the treatment group and there are no tests of statistical significance presented.

This study was included in the evaluation of vaccine effectiveness.

This study was included in the table of safety data.

Bashliaeva 1986 and Chumakov 1987

Both papers were translated from Russian and describe a prospective cohort study of a commercially available inactivated vaccine, Grippovac SE-AZH, in 3595 children aged three to six years of age. Chumakov re analysed the data because the total number of children participating had been wrongly calculated in Bashliaeva 1986 - the number of children receiving two doses had also been included in the number receiving one dose. The trial took place in Russia between November 1983 and May 1984. Children from 106 schools in two regions of Moscow were divided into four groups. One group received inactivated influenza vaccine, Grippovac SE-AZH Type 15, containing strains A/Brazil/11/78 (H1N1), A/Bangkok/1/79 (H3N2) and B/Singapore/222/79, at a concentration of 31.9 μg of hemagglutinin per dose. Another group received vaccine Grippovac SE-AZH Type 16, containing the same strains but at a concentration of 29.2 μg hemagglutinin per dose (due to less influenza B strain in the vaccine). Type 15 contained ovalbumin at a concentration of 0.125 μg/ml, whereas Type 16 contain 0.06 μg/ml ovalbumin. Two doses of vaccine were administered sub-cutaneously 28 to 30 days apart. Immunisation was carried out between November 1983 and January 1984; the two placebo groups were injected with physiological solution. The total number of children enrolled in the vaccine groups was 2274; 1398 received one dose of vaccine of which 127 were excluded from the trial after inoculation; 876 received two doses of vaccine 72 of whom were excluded from the trial after administration of the second dose. 1321 children were enrolled in the placebo groups of which 748 received one dose and 573 received two; 123 children were excluded from the trial after one dose and another 89 excluded after two doses of placebo.

The participants were followed up for three months after vaccination for incidence of influenza or acute respiratory illness; the paper did not mention whether the outcome assessment was blinded nor was the case definition defined. Regional surveillance data showed influenza types A (H1N1) and A (H3N2) with antigenic structures very similar to the strains contained in the vaccine were circulating during this period. While Bashliaeva 1986 describes the cases of somatic and infectious diseases as being twice as high ($P < 0.05$) in the vaccinated group, no data were presented so the figure has been disregarded for the purposes of this review. Chumakov 1987, did not calculate vaccine efficacy because of the

predominance of non-influenza acute respiratory illness (70%), determined serologically, found in the participants and the number of repeat occurrences of respiratory illness during the course of the winter. Chumakov 1987 refers to the studies taking place at 'internats' for which the nearest English translation is orphanage, raising questions about informed consent.

The data from Chumakov 1987 was included in the analysis of effectiveness.

Belshe 1992

This paper described a double-blind RCT of live cold-adapted trivalent influenza vaccine in children age 6 months to 13 years of age in USA. The year the study was carried out is not stated in the paper. Forty nine children were randomised to receive vaccine or placebo. Of the 34 vaccine recipients, 17 (aged 7 to 23 months) were triply seronegative to H1N1, H3N2 and B strains prior to vaccination and 15 (aged 10 to 116 months) were triply seropositive. Two children who were only singly or doubly seropositive where excluded from subsequent results. Seventeen children received the placebo. The vaccine contained strains A/Kawasaki/9/86 (H1N1) CR125, A/Korea/1/82 CR59 and B/Texas/1/84 CRB-87. The influenza A strains were both derived from a cold-adapted A/Ann/Arbor/6/60 parent virus and the B strain from cold-adapted B/Ann Arbor/1/66 parent virus. Strains CR125 and CRB-87 were diluted 1:100 and CR59 diluted 1:50 to give following concentration per 0.5 ml dose: H1N1 $10^{4.5}$; H3N2 $10^{4.4}$; B $10^{5.0}$ $TCID_{50}$. Each participant received one 0.5 ml dose of vaccine or placebo (vaccine diluent) administered intranasally. Following inoculation, children were observed in their own homes for 11 days by nursing staff. Nasopharyngeal swabs were taken daily for isolation of influenza virus and serum for antibody determination (not included in this review) was taken before and after inoculation. The safety outcomes recorded were fever - rectal temperature at least 38.3 ^{o}C or oral temperature at least 37.8 ^{o}C (in older children only); upper respiratory illness - rhinorrhoea on two consecutive days; lower respiratory illness - wheeze or pneumonia; and otitis media. Safety outcome data was presented separately for seronegative and seropositive responders but was combined for the table in this review. Significantly ($P < 0.05$) more rhinorrhoea was recorded in seronegative individuals than seropositive individuals but this was not significantly different to placebo, otherwise there were no significant differences between the responses of vaccine recipients and those receiving placebo. The authors concluded that the vaccine was well tolerated and safe when administered to young children.

This study was included in the table of safety data.

Belshe 1998

The paper describes a multi-centre RCT conducted in California, USA from August 1996 to April 1997 in 1602 children age 15 to 71 months old. The study compared one dose and two-dose regimes of cold-adapted trivalent influenza vaccine (manufactured by Aviron) with placebo. The vaccine contained the reassortant strains A/Texas/36/91-like (H1N1), A/Wuhan/359/95-like (H3N2) and B/Harbin/7/94-like in egg allantoic fluid with sucrose, phosphate and glutamate. The mean tissue-culture infective dose (TCID) of each strain was $10^{6.7}$. The strains matched the antigens recommended for that year by the Food and Drug Administration (1996 to 1997). The placebo consisted only of egg allantoic fluid with sucrose, phosphate and glutamate.

The vaccine and placebo were randomly assigned to sequential vaccine labels, the placebo is described as being indistinguishable from the vaccine in appearance and smell. The vaccine and placebo were administered intranasally using a spray applicator (0.25 ml per nostril). The two dose groups received a second dose of vaccine or placebo 60 days after the first dose. In the one-dose group, 189 participants were vaccinated and 99 received placebo; in the two-dose group 849 received vaccine and 410 placebo. Thirty-two children were randomised to received two doses of vaccine and received one, 23 children were randomised to received two doses of placebo and received one. Vaccine safety was monitored by asking parents to measure temperature daily for 10 days after vaccination using a digital thermometer provided by the study and record these on a diary card. Fever was defined as a temperature above 37.6 ^{o}C (axillary), above 37.7 ^{o}C (oral) or above 38.1 ^{o}C (rectal). The occurrence of specific symptoms - decreased activity, irritability, runny nose or nasal congestion, sore throat, cough, headache, muscle aches, chills and vomiting, were also recorded daily for 10 days.

The primary outcome of the study was the first episode of culture confirmed influenza in participants who became ill 28 days or more after dose one or immediately after dose two to the end of the influenza outbreaks in April 1997. Over the winter of 1996 to 1997, during which the trial was conducted, influenza A (H3N2) and influenza B were circulating in the population. The vaccine significantly reduced the occurrence of influenza in the study population, 14 of the 1070 children who received vaccine had culture-confirmed influenza compared with 95 of the 532 children who received placebo. Six children in the placebo group had two distinct influenza episodes cause firstly by A (H3N2) then by influenza B. Infection by both types was not found in the vaccinated groups. Vaccine efficacy was determined as follows: 87% for one dose of vaccine containing influenza A (H3N2); 91% of one dose of influenza B vaccine; 96% for two doses of influenza A vaccine and 91% for two doses of influenza B. The authors concluded that vaccine efficacy was equally high for older and younger children.

This study was included in the evaluation of vaccine efficacy.

This study was included in the table of safety data.

Study linked to Belshe 2000 and Piedra 2002.

Belshe 2000a

This study is the second year of the trial described in Belshe 1998. It included 1358 children aged 26 to 85 months of age who participated in the trial in the previous year, who were not re-randomised. The primary outcome was culture-confirmed influenza, with symptoms of infection appearing 28 days or more after vaccination. For this year the vaccine contained A/Shenzhen/227/

95-like (H1N1), A/Wuhan/359/95 (H3N2) and B/Harbin/7/94-like, 10^7 infective units of each strain were included per dose. Re-immunisation was carried out between September and November 1997; 917 children were given one dose of vaccine and 441 given one dose of placebo. Children were monitored for five months from the beginning of November. During this period there was an outbreak of A/Sydney/5/97 (H3N2) not included in the vaccine, which caused 15 cases of culture confirmed influenza in vaccinated children and 51 cases in the placebo group. Four cases of A/Wuhan/359/95-like were reported in the placebo group and one case of influenza B (strain not specified). No culture-confirmed infections by strains contained in the vaccine were found in the vaccinated group. Seventeen cases of otitis media associated with influenza A infection were reported from the placebo group compared with two from the vaccinated group. All eight cases of lower respiratory tract disease reported were from the placebo group.

Parents or guardians of each subject were given a digital thermometer and asked to record temperature and the occurrence of specific symptoms daily for 10 days on diary cards. The specific symptoms recorded were decreased activity, irritability, runny nose or nasal congestion, sore throat , cough, headache, muscle aches, chills and vomiting. Fever was considered a temperature > 100.6 ^{o}F rectal / 100.0 ^{o}F oral / 99.6 ^{o}F axillary. Serious adverse events occurring at any time during the trial were recorded by study personnel. Safety was monitored using the same method as year one of the study (Belshe 1998). Nineteen percent of vaccine recipients experienced runny nose or nasal congestion compared with 14% in the placebo group. Fever was observed in 2% of vaccinated children and 1.8% of those who received placebo.

This study was included in the evaluation of vaccine efficacy.

This study was included in the table of safety data.

Linked to Belshe 1998 and Piedra 2002.

Piedra 2002a

This paper describes in further detail safety data from the trial reported in Belshe 1998 and Belshe 2000a. Data is given for the same safety outcomes described above in Belshe 1998, vomiting, diarrhoea, abdominal pain and muscle aches are given for each of days 0 to 10 after the first dose in year one of the study. The incidence of runny nose and nasal congestion, irritability, decreased activity and fever are presented at days 2, 3, 8 and 9 after each dose in both years of the study. Data on following combinations of symptoms within 10 days of vaccination after each dose are given: at least two gastrointestinal symptoms; muscles aches and vomiting; diarrhoea and abdominal pain; vomiting and diarrhoea; vomiting and abdominal pain. Comparisons of antibiotic, antipyretic and antihistamine use within 10 days after vaccination showed a significantly (P < 0.05) higher use of antipyretic use in the placebo group after the first dose in year one of the study, otherwise there were no significant differences.

Afebrile illness, febrile illness, lower respiratory tract infection, otitis media, febrile otitis media, administration of oral antibiotics, analgesics / antipyretics, antihistamines / decongestants / antitussives 11 to 42 days after vaccination are presented for both years of the study. There was a significantly (P < 0.05) higher use of antihistamines / decongestants / antitussives in the placebo group in year two, otherwise there were no significant differences between outcomes in treatment and placebo groups.

Adjusted odds ratios for respiratory and gastrointestinal symptoms during the 10 days after vaccination showed runny nose or nasal congestion, vomiting, muscle aches and fever were significantly associated with the first dose of the live vaccine in year one of the study, for the second dose, runny nose only was significantly associated with administration of the live vaccine.

This study was included in the table of safety data.

Study linked to Belshe 1998 and Belshe 2000.

Beutner 1979a

Beutner 1979 is an RCT investigating the efficacy, effectiveness and safety of an inactivated influenza A vaccine containing the strain X-41 - A/Port Chalmers (H3N2) and a neuraminidase-specific recombinant vaccine of strain X-42, incorporating an equine-derived hemagglutinin component (Heq1) and N2 obtained from A/Port Chalmers. The study was conducted in USA over two winters from 1974 to 1976 in children aged 7 to 14 years.

Eight-hundred and seventy-five school children were randomised into three groups, 300 children in each vaccine group and 275 in the placebo group. One 0.5 ml intramuscular dose of vaccine or placebo was administered between September and November 1974. The follow up for efficacy and effectiveness was carried out until March 1976 although revaccination was not carried out in the winter of 1975 to 1976. During the follow up period there were outbreaks of influenza caused by the Port Chalmers strain in January and February 1974 and a minor outbreak of caused by A/Victoria strain from January to March 1976. Evidence of the Port Chalmers strain in the community was first demonstrated in Buffalo in mid-December 1974, at least one month after completion of the immunisations. The lengths and definitions of the epidemic periods are not stated. Determination of infection by influenza virus was determined serologically with a four-fold rise in H3 Port Chalmers-specific antibody considered a positive diagnosis of infection. No children were lost to follow up in the first year and all were included in the efficacy analysis.

In the second winter, 220, 201 and 185 children were included in the efficacy analysis for X-41, X-42 and placebo arms respectively. The efficacy of the vaccines in providing protection against infection during the Port Chalmers outbreak were 68.7% (X-41) and 37.4% (X-42). The efficacies of the vaccines against A/Victoria strain in 1976 were 80.0% (X-41) and 72.7% (X-42). The authors conclude that this data supports the role of neuraminidase-specific immunisation as the X-42 vaccine provided a similar degree of protection against the A/Victoria strain as the X-41 vaccine.

Vaccine safety was monitored for seven days following inoculation, any children reporting reactions through phone calls were examined by a physician and followed up for one to four weeks. Systematic reactions to vaccination presented were temperature

(100 to 103 ^{o}F or 104 ^{o}F and above), headache, nausea/vomiting, soreness/aching/chills. Local reactions presented were pain/tenderness at injection site, erythema and local swelling. Fever below 104 ^{o}F (40°C) was observed in 13% (X-41) and 14% (X-42) of children receiving vaccine compared with 1% of the children who received placebo.

This study was included in the evaluation of vaccine efficacy.

This study was included in the table of safety data.

Burtseva 1991

Burtseva 1991 was translated from Russian and describes a prospective cohort study of a monovalent live recombinant vaccine and bivalent inactivated vaccine. The study was carried out in 1987 to 1988 in 341 children aged 8 to 15 years from two Moscow schools. The live vaccine was obtained by recombination of the cold-adapted strain A/47/F (H3N2) with wild type A/Philippines/2/82, the concentration of infective units was 7.0 EID_{50}/0.2 ml. The commercially available (Omutninsk Chemical Factory) inactivated vaccine contained strains A/Philippines/2/82-like (H3N2) and A/Chile/1/83-like (H1N1), 10 mg of hemagglutinin per strain per 0.5 ml dose.

Four groups of children were formed (there was no reference to randomisation), one group was inoculated with live vaccine for two consecutive years; another with inactivated vaccine in 1987 and live vaccine in 1988; the third group received placebo in 1987 and live vaccine in 1988 and the fourth group received placebo both years. Two 0.5 ml doses of live vaccine were administered intranasally 21 days apart (information obtained from Alexandrova 1984 reference cited in paper) using a Smirnov sprayer. One 0.5 ml dose of inactivated vaccine was administered intramuscularly. A placebo was used but not described. Vaccine efficacy was assessed only for the 1987 inoculations based on the number of cases of influenza and ARI during the winter of 1987 to 1988.

Vaccine efficacy was monitored using two methods at each school. In school 1, cases from 1 January to 1 March 1988 were assessed from doctors' notes for non-attendance with diagnosis of ARI or influenza. For retrospective diagnosis, blood samples were taken during the convalescence period. An outbreak of ARIs began in December 1987 continuing to February 1988. In a sub-sample (77 children), 42% had influenza A (H3N2) diagnosed by seroconversion and 17% influenza B/Victoria/2/87. Influenza B was diagnosed in December 1987 and January 1988 and influenza A (H3N2) in January and February 1988. Thus the rise in cases in this school was first provoked by Type B and then by influenza A; close in antigenic structure to A/Sichuan/2/87 (H3N2). For vaccine efficacy, cases of illness due to influenza and ARI from 1 January to 1 March 1988 were analysed, excluding all instances of influenza B. In school 2, only laboratory confirmed cases of influenza A during the period of rise in cases (16 January to 15 February, 1988) were counted. Influenza A (H3N2) was diagnosed by hemagglutinin antibody inhibition (HAI) in 55 cases from 85 sick children (47.4%) and influenza B in 7 cases (6.0%). For the analysis of efficacy, children with laboratory confirmed influenza B were excluded.

This study was included in the analysis of efficacy.

This study was included in the analysis of effectiveness.

Ritzwoller 2005

This is a retrospective cohort study to assess the effectiveness of the 2003 to 2004 influenza vaccine in children in Colorado, USA. The study involved 5139 children aged 6 to 23 months who had at least one visit to the medical centre in the study in the 8 months prior to 1 October 2003. Children who received two influenza vaccinations at least 14 days before diagnosis of any influenza-like illness (ILI) or pneumonia and influenza (P & I) and at least one dose since September 2003 were classified as fully vaccinated. Children with no vaccination since September 2003 were classified as unvaccinated. Children who received two doses of vaccine since September 2003 but who sought medical attention within 14 days of the second dose or children who received only one dose since September 2003 and no previous vaccination were classified as partially vaccinated. The vaccine is not described in the paper but separate information gives the strains in the 2003 to 2004 vaccine as A/New Caledonia/20/99-like (H1N1), A/Moscow/10/99-like (H3N2) and B/Hong Kong/330/01-like. The two products licensed for children of these age group in USA at the time were inactive split-virion vaccines Fluzone (Aventis) and Fluvirin (Chiron). Data were collected from electronic medical records and the immunisation registry database for medically attended illnesses between 19 November and 7 December 2003. Vaccination status was included as a time-varying variable using a multivariate Cox proportional hazard model to estimate a hazard ratio (HR), this was used because patients continued to be vaccinated during the influenza season. Vaccine efficacy (VE) was calculated as one minus HR. The circulating strain during the study period was A (H3N2) and by 7th December 15% and 27% respectively of the participants were fully or partially vaccinated. The estimated hazard ratios were 0.75 (95% confidence intervals (CI) 0.56 to 1.00 for influenza-like illness and 0.51 (CI 0.29 to 0.91) for pneumonia and influenza. When fully vaccinated children were compared with unvaccinated the vaccine efficacy estimates were 25% for ILI and 49% for P & I. When partially vaccinated children were compared with unvaccinated, no statistically significant reduction in ILI and P & I was found. The authors report that the findings (and with an accompanying adult case-control study) support recommendations to continue vaccination despite a sub-optimal match between the circulating strain and the A (H3N2) strain in the vaccine. The study also provides further evidence that two doses of vaccine are needed to optimise protection.

This study was not included in the analysis (intraepidermic study), the data is presented in Additional table 17.

Clover 1991 - see Gruber 1990 (below)

Colombo 2001

Colombo 2001 is an RCT of an inactive subvirion vaccine in 344 pre-school children aged one to six years of age conducted in Sardinia between October 1995 and April 1996. No placebo was used

in this trial and participants were randomly assigned to receive the vaccine or no treatment. The vaccine, manufactured by Agrippal Biocine SpA contained 15 μg of highly purified surface antigens from influenza strains A/Johannesburg/33/94-like, A/Singapore/6/86-like, B/Beijing/184/93-like. Two doses of vaccine were administered one month apart. The vaccines were administered between mid-October and mid-November 1995. Based on previous experience of the influenza season in Sardinia, participants were followed up for five months from 1 December 1995 to 30 April 1995. The outcome measured was influenza-like illness defined as a temperature of 38.5 ^{o}C (rectal, measured by a paediatrician) and cough or sore throat lasting at least 72 hours. Influenza-like illness was observed in 22 of 177 participants in the treatment group and 63 of 167 participants in the no treatment group, the reduction in disease incidence was therefore 67%. No information is presented on any circulating strains of influenza virus. Nine children from the vaccinated group were absent from school for longer than four days compared with 62 children from the no treatment group. Three children experienced otitis media in the no treatment group and none in the vaccinated group. Safety data was recorded; two children experienced fever and malaise after vaccination and two erythema at the injection site but there was no placebo data for comparison.

This study was included in the evaluation of vaccine effectiveness.

This study was included in the table of safety data.

Desheva 2002

The paper was translated from Russian and describes an RCT of a live trivalent influenza vaccine carried out in Russia during the winter 1999 to 2000 in 256 children aged three to six years of age. The vaccine used was an adult variant of a live influenza vaccine containing the 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. The difference between 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). The attenuation donor for influenza B virus was the same for both the adult and child variants. The children's vaccine needs to be administered twice whereas adult is only once. The aim of the study was to test the adult variant in children as a single dose. Three groups of children were formed by random selection, two to receive the one dose vaccine and another one dose of the placebo - lyophilised allantoic fluid. The total number of children who received vaccines was 182 and 68 received placebo. Participants were inoculated intranasally with a 0.5 ml dose using an RDZH-M4 sprayer. Medical examination of each child was carried out daily for five days after inoculation; temperature was measured and any local and general reactions recorded. The effectiveness outcomes presented were morbidity due to influenza or acute respiratory illness and bronchitis within six months of inoculation. The safety outcomes presented were temperature (up to 37.5 ^{o}C; 37.6 to 38.5 ^{o}C; 38.6 ^{o}C and above), headache, and catarrh (all within five days of inoculation) and infection (excluding influenza and acute respiratory illness), somatic illnesses and allergies (within six months). Other outcomes in this study were the determination of genetic stability of the vaccine by re-isolation of virus from participants and serum antibody response to vaccination, neither of which are included in this review.

The authors found a statistically significant ($P < 0.001$) reduction in morbidity due to influenza and acute respiratory illnesses among vaccinated group compared with the placebo group. No moderate or severe temperature reactions were observed after inoculation and no statistically significant differences were observed in the frequency of weak temperature reactions between those participants who were vaccinated and those who received the placebo. The general and local reactions which occurred disappeared within three days. The authors concluded that the adult variant could be recommended for children from the age of three years administered once intranasally.

This study was included in the table of safety data.

El'shina 2000

El'shina 2000 was translated from Russian and describes a trial of an inactivated polymer subunit vaccine 'Grippol' carried out in Russia from October 1997 to April 1998. Safety and reactogenicity was evaluated in a randomised controlled trial carried out in 3290 children of two age groups. Thirty children aged 14 to 17 years received vaccines and 30 no treatment; after the results of reactogenicity were obtained for this group, two groups of children aged 6 to 14 were randomised, 40 in each group. One group received the vaccine and the other group no treatment. The vaccine included unidentified strains of influenza A (H1N1), A (H3N2) and B; containing 5 μg of hemagglutinin of each strain and 500 μg of polyoxidonium (immuno-stimulator) and was administered sub-cutaneously in a 0.5 ml dose. Headaches, cough, sore throat, head cold and generally feeling unwell were recorded for five days after inoculation. Effectiveness of the vaccine was evaluated in a prospective cohort study of 3150 children aged 6 to 14 years; 1835 children were enrolled on the vaccine arm but 905 were not vaccinated, but still followed up; 1315 children were allocated to the main control group. Data on morbidity due to influenza and ARI (clinically diagnosed) was collected from December 1997 to April 1998. During this period there was a seasonal rise in morbidity due to influenza and ARI. The circulating influenza strain was not identified. There were statistically ($P < 0.05$) higher morbidity (30.9%) in the no treatment group compared with the vaccinated group (15.7%). The authors give an efficacy index but this was calculated by dividing the morbidity data by the percentage of positive influenza identifications determined serologically from a sub-group of 53 individuals so has not been considered in our analysis. There were no statistically significant differences between groups for the safety outcomes considered; the efficacy cohort was monitored for upper respiratory illness (excluding ARI), other infectious disease, gastrointestinal illness, skin diseases, allergies and cardiovascular disease - incidences were rare and there was no difference between vaccinated and unvaccinated groups.

This study was included in the analysis of effectiveness as a cohort study.

This study was included in the table of safety data as an RCT.

Grigor'eva 1994 see Rudenko 1996a (below).

Grigor'eva 2002

Grigor'eva 2002 describes an RCT of two live vaccines which was conducted in Russia in 2486 children during the winter 1999 to 2000. This study was translated from Russian. Healthy school children aged 7 to 14 years were selected from four schools by medical staff. After obtaining written consent from parents, participants were randomised into six groups. Two groups received two doses of a children's variant of live vaccine which had been further attenuated than the adult variant; one group received two doses of placebo as the corresponding control. Two groups received one dose of the adult variant of the live vaccine with another group receiving one dose of placebo as the control. Both variants of the vaccine contained the same influenza strains - A/Peking/262/95 (H1N1), A/Sydney/5/97 (H3N2) and B/St Petersburg/95/20, the number of infective units per 0.2 ml was at least $10^{6.5}$ for type A viruses and $10^{6.0}$ for type B virus. Both vaccines were administered intranasally, 0.25 ml per nostril, using a sprayer. The placebo used was lyophilised allantoic fluid. Participants in the two dose groups received the doses 21 days apart. The group randomised to receive two doses of the children's vaccine consisted of 675 participants with 369 in the corresponding two dose placebo group (from the reactogenicity data - symptoms of ARI $\leq$ seven days after vaccination - presented). Efficacy data is presented with 539 in the treatment group and 297 in the placebo group, therefore 136 from the treatment group and 72 from the placebo group either did not receive the second dose or were lost to follow up. In the adult vaccine arm, 971 children received one dose of vaccine and 471 received one dose of placebo, the total numbers of participants are the same in the reactogenicity and efficacy data presented. The outcomes measured in the study were numbers of children with influenza or acute respiratory infection diagnosed clinically during the total epidemic period, 10 January to 1 February 2000, and during the peak in morbidity between 31 January and 6 February 2000. The influenza epidemic was caused by strain A/Sydney/5/97 (H3N2) which was included in the vaccine. The safety outcomes measured were numbers of children consulting a doctor within seven days of vaccination with either symptoms of acute respiratory infection or with an allergic reaction.

This study was included in the analysis of effectiveness.

This study was included in the table of safety data.

Gruber 1990

Gruber 1990 describes an RCT of a commercial inactivated subvirion vaccine and a live vaccine carried out in USA in 1985 to 1986. One hundred and eighty-nine children aged 3 to 18 years of age were enrolled in the study. The commercial inactivated vaccine, Fluogen (Parke Davis) contained 15 μg of each of strains A/Chile/83 (H1N1), A/Philippines/82 (H3N2) and B/USSR/83 each per 0.5 ml dose. The live vaccine contained $10^{7.3}$ infective units per 5 ml dose of strain A/Korea/1/82 (H3N2) (CR59) and $10^{6.3}$ per dose of strain A/Dunedin/6/83 (H1N1) (CR64). Efficacy and effectiveness data is presented for the inactivated vaccine. Fifty-eight children aged 3 to 18 years were randomised to receive the live vaccine, 54 children received inactivated vaccine and 77 received placebo. The data are presented in three age groups - 3 to 5 years; 6 to 9 years and 10 to 18 years. Children randomised to the placebo groups received either 0.5 ml buffered saline intranasally or 0.5 ml sterile saline intramuscularly, but only combined placebo data was presented. When community surveillance, carried out by the Influenza Research Center, indicated the virus was present in the community, weekly phone calls were made to participating families. Follow up of participants was carried out for six months after vaccination to the end of the influenza season in 1986. Infection with the circulating influenza B strain in recipients of the inactivated vaccine (which included an influenza B strain) was determined in two ways - firstly - infection determined by positive viral culture and secondly - illness occurring in a child within 10 days of isolation of virus in a household contact and accompanied by a post-season antibody rise. No efficacy and effectiveness measure was determined for participants in the live vaccine arm. The protection given by the B/USSR component of the inactivated vaccine was 62% compared with placebo. Safety outcomes were assessed for fourteen days following inoculation. Local reactions to intramuscular injection occurred in 20% of the vaccine recipients and 19% of controls. Upper respiratory tract infections (rhinorrhoea and nasal congestion) occurred in 15% of live vaccine recipients and 19% of intranasal placebo recipients.

This study in include in the analysis of efficacy.

This study was include in the table of safety data.

Clover 1991

Clover 1991 describes the second year of the multicentre double-blind RCT described in Gruber 1990. The study took place in USA over the winter 1986 to 1987. Seventy percent of the study population (194 children) participating in the second year had taken part in year one and were not re-randomised. The live vaccine contained strains A/Bethesda/1/85 (H3N2) (CR90) and A/Texas/1/85 (H1N1) (CR98) each at a concentration of 10^7 infective units per dose; the A/Texas strain was antigenically similar to A/Chile/1/83 (H1N1). The inactivated vaccine contained A/Chile/83 (H1N1), A/Mississippi/85 (H3N2) and B/Ann Arbor/86, 15 μg each per dose (0.5 ml). The study included infection of contacts of vaccine recipients as an outcome and 98 families, including 202 children aged 3 to 18 years (20 of these under 3 years old), and 257 adults completed the study. Fifty-eight children aged 3 to 18 years received the live vaccine, 54 the inactivated vaccine and 82 the placebo. Two children from the live vaccine group were lost to follow up (either moved from the study area or would not provide blood samples). When ongoing surveillance indicated influenza virus was spreading in the community, weekly telephone calls were made to participating families to evaluate respiratory illnesses. Final blood specimens were

collected two weeks after surveillance indicated that the epidemic had ended. The length of the epidemic period was not stated.

The primary outcome measure was influenza infection which was determined by either a positive viral culture or a post-season rise in antibodies in an individual who was ill within 10 days of a household contact who had a positive viral culture. Secondary outcomes were influenza A in family contacts and consequences of influenza infection in vaccinated individuals - afebrile or upper respiratory tract infection; febrile or influenza-like symptoms; otitis media and lower respiratory tract infection. The circulating strain of influenza was A/Taiwan/86 (H1N1) which was not included in either vaccine. Infections with A/Taiwan/86 were observed in 44% of 82 children who received placebo and 21% of 56 children who received the live vaccine giving a protection rate of 51% ($P < 0.05$). Seventeen percent of children who received the inactivated vaccine were infected, giving a protection rate of 62% ($P < 0.05$). In children aged 3 to 9 years, two doses of live vaccine given one year apart to 17 participants gave 74% protection against infection and 81% protection against illness associated with infection. For the inactivated vaccine the rates of protection in 30 participants were 56% for both infection and illness associated with infection. In children aged 10 to 18 years, 24% of individuals who received live vaccine were infected but no infections were observed in the group who received the inactivated vaccine.

The authors concluded that the inactive vaccine gave better protection against infection in older children than the live vaccine. Younger children aged three to nine were, however, offered better protection by the live vaccine. There were no statistical differences in infection rates for family contacts of children receiving either vaccine or placebo.

This study was included in the evaluation of vaccine efficacy.

This study was included in the evaluation of vaccine effectiveness.

Gruber 1996

This paper describes an RCT carried out in USA over the winter 1991 to 1992. The study was carried out in 182 children aged 6 to 18 months born after the last outbreak of influenza. The participants were randomised to receive one of three live attenuated vaccine preparations (Wyeth-Ayerst) or placebo. The live vaccines were monovalent A/Kawasaki/9/86 (H1N1) containing $10^{6.2}$ infective units per dose; monovalent A/Los Angeles (H3N2) containing $10^{6.2}$ infective units per dose and divalent vaccine containing both of the above strains at the same concentration; allantoic fluid was administered as the placebo. Forty-four children were included in the results having received the H1N1 vaccine; 45 the H3N2 vaccine; 47 the bivalent vaccine and 44 the placebo. The diary information for two vaccinated children was unavailable but it is not stated from which arm of the study. Each participant received one 0.5 ml dose intranasally. The outcomes measured were symptoms of influenza-like illness and virus isolation data which were not reported; rise in antibodies (not considered in this review) and the following safety outcomes: fever, cough, rhinorrhoea, otitis media and diarrhoea with 10 days of vaccination. The data was collected in a double-blind manner. Parents were asked to contact the study site if a child had one of more symptoms on a given day or had fever, defined as a temperature above 37.8 ^{o}C; these children were clinically evaluated. There was no significant difference in the frequency of mild respiratory symptoms and low-grade fever between the treatment and placebo groups and diarrhoea and otitis media were uncommon in all groups.

This study was included in the table of safety data.

Gruber 1997

This paper describes an RCT of a cold-adapted, live attenuated influenza A (H1N1 and H3N2) vaccine at three different concentrations in 1126 children aged 2 to 36 months. The study took place in USA, autumn 1993, at 13 participating institutions and included 635 children aged 2 to 18 months and 491 children aged 19 to 36 months. The vaccine used contained the strains A/Kawasaki/9/86 (H1N1) and A/Beijing/352/89 (H3N2) and participants were randomised in a double-blind fashion to receive one of three doses, 10^4,10^6 or 10^7 infective units per 0.5 ml dose or placebo (allantoic fluid) in a ratio 3:3:3:1. However in Table 01, showing fever reported within seven days of vaccination, the sum of the denominators is 1249 (1125 receiving vaccine and 124 receiving placebo) and are broken down as follows: for the age group $\leq$ 6 months, 53 children received the 10^4 dose, 60 the 10^6 dose, 49 the 10^7 dose and 19 placebo. In the 7 to 18 months age group, 136 children received the 10^4 dose, 131 the 10^6 dose, 145 the 10^7 dose and 44 the placebo. In the > 18 months age group, 189 children received the 10^4 dose, 176 the 10^6 dose, 186 the 10^7 dose and 61 the placebo. Participants each received one 0.5 ml dose administered intranasally and were followed up for seven days after inoculation by using diary cards kept by parents. Parents notified the study centre if a child had more than one symptom on any given day and/or fever. The outcomes were fever (temperature at least 38.6 ^{o}C rectal; 38.1 ^{o}C oral or 37.5 ^{o}C axillary) and respiratory symptoms, namely cough, pharyngitis, rhinorrhoea and any other. Serum antibody levels were determined but are not included in this review. There were no statistically significant differences between vaccine or placebo groups for either fever or respiratory symptoms.

This study was included in the table of safety data

Gutman 1977

Gutman 1977, describes a placebo-controlled trial of inactivated whole and split-virion vaccines of different concentrations produced by four manufacturers. The study was carried out in 100 children in USA in May and June 1976. Thirteen vaccines were evaluated in 67 children aged 6 to 10 years, three of these vaccine were also evaluated in 43 children aged 3 to 6 years. Vaccines were allocated by continuous rotation of vial numbers, all contained the strain A/New Jersey/76 (H1N1) and were administered intramuscularly as a single 0.25 ml dose. The vaccine were manufactured by Merrell-National (MN), Wyeth (W), Parke Davis (PD) and Merck Sharp and Dohme (MSD). The concentrations ranged from 100 to 400 CCA units per dose; five vaccines (MN and

MSD) were whole virus preparations and eight vaccines (W and PD) were split-virion preparations. In the 3 to 6 year age group, 9 children received MN100, 12 received W100, 10 received PD100 and 12 received placebo. In the 6 to 10 year age group, six children received MN100, six received MN200, five received MN400, six received MSD100, six received W100, six received W200, eight received W800, four received PD100, six received PD200, eight received PD400 and six received placebo.

Follow up was carried out for only one day following inoculation. The primary outcome measure was fever ($\leq$ to 38 ^{o}C, $\leq$ 38.5 ^{o}C and $\leq$ 39 ^{o}C), parents recorded temperature and reported any adverse reactions. The participants were all examined at the study centre one day after inoculation for any adverse reactions or fever. Other outcomes were headache, malaise, stomach ache and local reactions. Antibody increase in serum samples was measured in this study but is excluded from this review. The authors reported that reaction to the vaccines in the three to six years age group was minimal, a lump at the injection site was reported in two children out of 34 children who received vaccine and three children had a temperature less than 38 ^{o}C. In the older age group, one child had a temperature of 39.9 ^{o}C and another of 38.3 ^{o}C, the former had no symptoms of fever, the latter had purulent otitis media. Twelve of the 64 children aged 6 to 10 years who received the vaccine developed a palpable lump at the site of injection. There was no mention of randomisation in the text so this has been classified as a cohort study.

This study was included in the table of safety data.

Hirota 1992

Hirota 1992 describes a case control study carried out in Japan in 1988 to 1989. The retrospective study looked at the risk factors associated with influenza-like illness in 814 school children aged 6 to 12 years. Questionnaires were given to parents during the last week of the peak of an influenza epidemic on 11 February 1989. Respondents were asked to note any symptoms of acute respiratory illness over the previous five weeks, including fever, and the actions taken as a result of these symptoms: medicine administered, consulting a doctor, absence from school. Preseason vaccination status for each child was obtained from school records. The vaccine administered over this period was an inactivated, commercially available vaccine containing strains A/Yamagata/120/86 (H1N1), A/Fukuoka/C29/85 (H3N2), A/Sichuan/2/87 (H3N2) and B/Nagasaki/1/87 administered subcutaneously in two 0.3 ml doses (dose one 25/10/88, dose two 16/11/88). The primary outcome was severe influenza-like illness (S) which was defined as a temperature of 39 ^{o}C or above accompanied by absence from school and medical consultation.

The circulating influenza virus was predominantly H1N1 and 90% of the virus isolated was antigenically similar to the A/Yamagata/120/86 (H1N1) strain included in the vaccine. There was a sharply defined epidemic peak from 25 December 1988 to 11 February 1999, however, schools were closed until 7 January so illness was recorded from 8 January until 11 February 1989.

The authors found that vaccination was inversely associated with SILI risk but not with the risk of mild influenza-like illness (MILI) but did not present immunisation data for MILI. Also, the case definition omits onset of ARI during the first two weeks of the epidemic peak and after the peak, which could enhance the conservative determination for the risk factor. The criteria for the selection of case and controls (i.e. absenteeism and medical consultation) might have also introduced a selection bias.

This study was included in the analysis of effectiveness.

Hoberman 2003a

Hoberman 2003 describes an RCT of inactivated vaccine for prevention of influenza and acute otitis media (AOM) in 786 US children aged 6 to 24 months. The study took place over two winters from 1999 to 2001. A separate cohort was enrolled for each winter. Children were randomly assigned in blocks of nine within the following strata: prone to acute otitic media (AOM) ($\geq$ 3 episodes AOM in $\leq$ 6 months or $\geq$ 4 episodes in $\leq$ 12 months); attending day care (exposure to $\geq$ 3 non-family children for $\geq$ 10 hours per week); received one dose or more of pneumococcal conjugate vaccine (cohort two only). The vaccine used was commercially available Fluzone (Aventis Pasteur) administered in two 0.25 ml doses four weeks apart. In 1999 to 2000 the vaccine contained strains A/Beijing/262/95 (H1N1), A/Sydney/15/97 (H3N2) and B/Yamanashi/166/98. In 2000 to 2001 the vaccine contained A/New Caledonia/20/99 (H1N1), A/Panama/2007/99 and B/Yamanashi/166/98. The placebo used was standard diluent (Aventis Pasteur). In 1999 to 2000, 278 children received the vaccine of which 246 completed the trial; of the 139 placebo recipients 127 completed the trial. In 2000 to 2001, 253 children received the vaccine and 232 completed the trial; 123 received placebo of which 114 completed the trial. Cohort 1 (enrolled 1999) was followed up through bi-weekly visits until the end of the respiratory season (31 March 2000) then monthly visits until 15 November 2000. Cohort 2 (enrolled 2000) was followed up through bi-weekly visits until 31 March 2001. Data were collected in a double-blind manner. Parents were instructed to contact study staff if a child had any symptom or sign of upper respiratory infection or AOM and an interim visit was arranged. A throat culture to diagnose influenza was performed on patients with symptoms and signs of upper respiratory tract infection with fever ($\geq$ 38 ^{o}C), AOM or both. Monitoring of unexpected adverse events was conducted at each visit by reviewing a child's medical record and interviews with parents. Minor adverse reactions (for example injection site reactions, low-grade fever) were not recorded. Health care utilisation by participants was determined from interviews with parents.

The outcomes measured were episodes of culture proven influenza; episodes of AOM during the respiratory season (1 December to 31 March) and influenza seasons; middle ear effusion and socioeconomic outcome. These included visits to primary care physicians, emergency departments, hospital admission, antibiotics administered, illness in family members, parents missing work and

parents making other than usual care arrangements. In 2000, the influenza season was defined as the six week period (3 January to 15 February 2000) during which 25 (67%) of culture proved cases of influenza occurred. In 2001, influenza was infrequent and no clustering of cases was observed; the season was defined as a 13 week period (4 January to 30 March 2001) during which 11 (85%) of culture proven cases were confirmed. In 2000, the circulating influenza strains were A/Beijing and A/Sydney and in 2001 the circulating strains were A/New Caledonia, A/Panama and B/Yamanashi. The paper reports that the vaccine and circulating strains were well matched for both years of the study.

The authors conclude that the efficacy of the vaccine against culture-confirmed influenza was 66% in 1999 to 2000 and -7% in 2000 to 2001, but influenza attack rates differed in each year (influenza in the placebo groups was 15.9% and 3.3% respectively). The vaccine did not reduce either the proportion of children with at least one episode of AOM during the respiratory season; the monthly rate of AOM, estimated time with middle ear effusion or utilisation of health resources. No safety data were presented but the authors state that the vaccine was well tolerated.

This study was included in the analysis of efficacy.

Jianping 1999

Jianping 1999 describes a cohort study of Vaxigrip (Pasteur Mérieux) inactivated vaccine carried out in China from December 1996 to May 1997. The study was carried out in families in the Chinese Army from three age groups; 3 to 6 years, 18 to 59 years and over 60 years. One-hundred and sixty-eight children participated in the study, 80 were vaccinated and the corresponding control group was made up of 88 unvaccinated children. Vaccinated children received two 0.25 ml doses administered one month apart; the route of administration (intramuscular or subcutaneous) was not described. Vaxigrip is a split-virion trivalent vaccine but the strains included were not given. Participants were observed from 21 days to 6 months after inoculation and asked to report temperatures over 38.5 ^{o}C and other symptoms. Acute respiratory illnesses were recorded throughout a follow up period from 21 days to 6 months after vaccination. There was no influenza season defined or circulating strains specified. The outcomes were classified as follows: flu-like syndrome - simultaneous temperature over 38.5 ^{o}C with headache, myalgia or arthralgia; common-cold symptoms - fever of 38.5 ^{o}C or above, headache, myalgia or arthralgia, cough, rhinorrhoea and sore throat but excluding symptoms of flu-like syndrome; upper-respiratory infections - flu-like syndrome and cold symptoms. The paper reports a significant reduction, 84.8%, in the incidence of influenza-like symptoms in children. Symptoms were only counted once during the follow up period. A 35% reduction in common cold symptoms was observed and a 41% reduction in upper respiratory infections. Statistical analysis using Chi-squared was presented for the combined age groups only but the authors report that there were virtually no difference in between age groups. The authors state that no serious adverse events were reported and conclude that Vaxigrip can provide good protection against influenza and the common cold, however, it is stated there is little risk of influenza infection during the winter in Beijing.

This study was included in the analysis of effectiveness

Kawai 2003

This paper describes an Internet-based cohort study on the effectiveness and safety of inactivated influenza vaccine in Japan over the 2001 to 2002 season. Thirty-eight clinics participated in the study for which 1553 children aged 0 to 15 years were enrolled over a three month period from October to December 2001. The study included adults and older children but the data for children 16 years and older was grouped with adults. The trivalent vaccine contained strains A/New Calendonia/20/99, A/Panama/2007/99 and B/Johannesburg/5/99 (30 mg antigen of each) and the volume of vaccine varied depending on age. Children below 1 year received 0.1 ml; from 1 to 6 years 0.2 ml, from 6 to 13 years 0.3 ml and 14 years and above 0.5 ml. The vaccine was administered either once or twice as requested by the subject. The number of children vaccinated twice, once or not vaccinated respectively for each age groups were as follows: 0 to 3 years - 216, 36, 93; 4 to 6 years - 258, 46, 64; 7 to 9 years - 201, 65, 58; 10 to 12 years - 143, 31, 52 and 13 to 15 years - 181, 73, 36. The interval between inoculations for those receiving two doses was between one and four weeks. Unvaccinated control participants were matched by clinic and gender and as closely as possible by age to vaccinated participants. The end of the follow up period was 31 May 2002 over which the effectiveness of the vaccine was evaluated. There was no defined influenza season given and circulating strains were not specified.

Most clinical symptoms were collected by self-reporting questionnaire, some were obtained by phone or mail. Information was entered onto the Internet-based system by doctors after the end of the influenza season. Study outcomes were as follows: influenza-like illness - sudden onset fever above 38 ^{o}C, sore throat (as symptom of URTI) and general fatigue; influenza - ILI with positive results from rapid diagnosis kits based on enzyme immunoassay or immunochromatography. Vaccine efficacy in preventing influenza was reported as 54.0% ($P < 0.05$ between vaccinated and unvaccinated) in children receiving one dose and 79.8% ($P < 0.01$) in those who received two doses. Effectiveness at preventing influenza-like illness was 67.6% in children receiving one dose ($P < 0.01$) and 84.5% in those receiving two doses ($P < 0.01$).

This study was included in the analysis of efficacy.

This study was included in the analysis of effectiveness.

Khan 1996

Khan 1996 describes an RCT to compare the effectiveness of a live and an inactivated vaccine in 555 Russian school children aged 9 to 12 years carried out over the winter 1991 to 1992. The route of administration, intramuscular or intranasal, was chosen by parents but children were randomised to receive either vaccine or placebo using a block randomisation with a vaccine to placebo ration of 2:1. The inactive vaccine was administered intramuscularly except

for an unknown number that were administered sub-cutaneously by mistake. The recombinant live vaccine (Odessa Production Company) was produced using the donor strains A/Leningrad/134/17/57 H2N2 and B/Leningrad/14/55 with wild type strains A/Leningrad/92/89 H1N1, A/Zakarpatje/354/89 H3N2 and B/Yagamata/16/88. The vaccine contained 7.0 - 7.5 $\log_{10}$ EID_{50} of each virus per 0.5 ml dose. The inactivated vaccine use was a commercially available (Wyeth-Ayerst) split-virus preparation containing 15 μg of hemagglutinin from each of strains A/Taiwan/1/86 (H1N1), A/Shanghai/16/89 (H3N2) and B/Yamagata/16/88. The intranasal placebo was egg allantoic fluid and the intramuscular placebo was normal saline. All participants received a single dose of vaccine or placebo. Two hundred children received the live vaccine of which 196 were included in the analysis, 168 received inactivated vaccine of which one was lost to follow up. One hundred children received intranasal placebo and 87 intramuscular; there were no losses to follow up. From 1 January to 2 February 1992 there was an epidemic of an unspecified strain of influenza A (H3N2) according to the Vologda Medical Council; the definition of the epidemic is not given.

Influenza and ARI data were combined for placebos so were split (100:87) for the purposes of this review. The primary outcome of the study was absence from school, defined as the first school absence with physician's diagnosis of either acute respiratory disease or influenza during the epidemic period 1 January to 2 February 1992.

Participants were monitored for four days or one day following inoculation. One case of fever (37.5 to 37.9 ^{o}C) was observed in the live vaccine group. Twenty-two cases of low fever (up to 37.4 ^{o}C) were observed in all groups. Local reactions were observed in 27% of the inactivated vaccine group. Coryza (12%) and sore throat (8%) were observed in the live vaccine group.

This study was included in the analysis of effectiveness.

This study was included in the table of safety data.

King 1998

King 1990 describes an RCT of a live, cold-adapted, trivalent influenza vaccine in 256 children aged 18 to 71 months. The study took place in USA and Chile over the winter November 1995 to May 1996. In USA, 258 children were enrolled onto the study and 118 were enrolled in Chile. The vaccine contained cold-adapted strains A/Texas/36/91 (H1N1), A/Johannesburg/33/94 (H3N2) and B/Panama/45/90 and was prepared in four concentrations of 10^4, 10^5, 10^6 and 10^7 infective units ($TCID_{50}$). The trial took place in three stages in each country. The first groups were randomised to receive 10^4, 10^5 or placebo, the second groups to 10^6 or placebo and the third groups to 10^7 or placebo. In total, 58 children received the 10^4 dose, 56 the 10^5 dose, 56 the 10^6 dose, 63 the 10^7 dose and 122 received the placebo. The vaccine was administered intranasally by dropper or spray device (producing a large particle aerosol) in USA and by spray device alone in Chile. After inoculation, parents recorded evening temperature and presence of the following reactions: cough, wheezing, rhinorrhoea, sore throat or irritability daily for 10 days. Children were examined by clinician if they had fever (axillary, oral or rectal temperature > 38 ^{o}C) or any two of above symptoms. Serum antibody levels were determined but are not included in this review. No significant differences in the frequency of reactions were detected at any dose compared with placebo and the authors concluded that the vaccine was safe and well-tolerated in children of this age group, even at the highest dose.

This study was included in the table of safety data.

Levine 1977

This paper describes a randomised double-blind trial of four inactivated whole and split virion vaccines produced by different manufacturers (Parke Davis (PD); Wyeth (W); Merrell National (MN); Merck, Sharpe, Dohme (MSD)) conducted in USA, 1976. The study was carried out in children aged three to five years, the number enrolled is not stated but 160 children were included in the analysis. All of the vaccines contained strain A/New Jersey/8/76 (H1N1), the split virion vaccines (PD and W) were tested at three concentrations (50, 100 and 200 CCA) and the whole virus vaccines (MN and MSD) at two concentrations (50 and 100 CCA). Children were inoculated with one dose of an unspecified volume of vaccine administered intramuscularly between May and July, 1976. The numbers of children receiving each vaccine were as follows: PD50 - 4; PD100 - 16; PD200 - 5; W50 - 4; W100 - 14; W200 - 5; MN50 - 22; MN100 - 22; MSD50 - 22, MSD100 - 13 and placebo 33. A two dose arm of the study was set up but the data have not been extracted as the placebo recipients received vaccine as a second dose so there is no comparator. Parents were supplied with a thermometer to record temperatures at 6, 9 and 24 hours after inoculation and recorded any adverse reactions over the 24 hour period (Lerman 1977). Nausea and malaise are also presented as outcomes. Serum antibody levels were determined but are not included in this review. Whole virus vaccines were frequently associated with low grade fever (100 to 101 ^{o}F). The split-virus vaccines were less reactogenic, but no statistical comparison between vaccines and placebo is presented.

This study was included in table of safety data.

Maeda 2002

Maeda 2002 describes a cohort study on the efficacy of inactivated vaccine carried out in Japan between November 1999 and April 2000. Eight-six children, 5 to 83 months old on recruitment received two doses of vaccine 14 days apart during November and December 1999. Ninety-four aged matched children not vaccinated within one year of enrolment and randomly assigned from medical records formed the control group. The vaccine contained the strains A/Beijing/262/95 (H1N1), 200 chick cell agglutination units (CCA)/ml; A/Sydney/5/97 (H3N2), 350 CCA/ml and B/Shandong/7/97, 300 CCA/ml and was administered sub-cutaneously. Children under one year received 0.1 ml per dose, those one to six years 0.2 ml and those older than six years 0.3 ml.

Follow up took place from January to April 2000. The primary outcome was influenza A infection. Children with febrile illness (>

37.8 ^{o}C) visited hospital, were given a physical examination and had throat swab taken. Swabs were tested for influenza A infection by enzyme immunoassay membrane test (Directigen FLU-A, Becton Dickenson). Questionnaires were sent to all participants regarding febrile illness during the follow up period or interviews were carried out at the end of the study period. The only outcome reported in the paper is confirmed influenza A infection during the follow up period from January to April, 2000. The influenza season was not defined and any circulating strains of influenza virus not specified. The prevalence of influenza A in the group receiving vaccine (5.8%) was significantly lower (P = 0.016) than the control group (17.0%) but the authors report that four out of five infected children in the vaccine group were under two years old and conclude that the vaccine reduces the incidence of influenza A infection in two to six year old children.

This study was included in the analysis of efficacy.

Maeda 2004a

Maeda 2004 describes a cohort study of inactivated influenza vaccine in 346 children aged 6 to 24 months carried out in Japan between January 2000 and April 2002. The rationale behind the study was that many cases of influenza-associated encephalitis-encephalopathy had been reported since a vaccination programme ceased in 1994 giving rise to a debate as to whether vaccine should be given to young children and infants. Vaccine was given to 175 children in November or December 1999, 2000 or 2001. As a control group, 171 aged matched, unvaccinated (within one year of enrolment) children were randomly assigned from medical records; placebo vaccines were not administered for ethical reasons. Children under 12 months received one 0.1 ml dose of vaccine sub-cutaneously; children aged 12 to 24 months received one 0.2 ml dose. In 1999/2000 the vaccine contained 200 CCA/ml of A/Beijing/262/95 (H1N1) and 350 CCA/ml of A/Sydney/5/97 (H3N2) and B/Shandong/7/97. In 2000 to 2001 the vaccine contained more than 15 μg hemagglutinin/0.5 ml of A/New Caledonia/20/99 (H1N1) A/Panama/2007/99 (H3N2) and B/Yamanashi/166/98. In 2001/2002 the vaccine contained more than 15 μg hemagglutinin/0.5 ml of A/New Caledonia/20/99 (H1N1), A/Panama/2007/99 (H3N2) and B/Johannesburg/5/99. The circulating viruses in each year were not specified and only influenza A was tested for. No definitions of lengths of epidemic periods were given.

Participants were followed up from January to April each year. If children had a temperature of over 38 ^{o}C a throat swab was taken and tested for influenza A using a commercially available antigen test (Directigen FLU-A, Becton Dickenson). None of patients infected with influenza A required hospitalisation or developed serious influenza complications. Attack rates between the treatment and control group were not significantly (P = 0.117) different and the authors concluded that the vaccine did not reduce the attack rate of influenza A in 12 to 24 months old children.

This study was included in the analysis of efficacy.

Nicholls 2004

Nicholls 2004 describes a retrospective cohort study of vaccine efficacy during an outbreak of influenza A (H3N2) in a highly vaccinated, semi-enclosed religious community in UK during the winter 2001 to 2002. The study was carried out in ages 0 to > 65 years. The number of cases were presented in age groups but did not include denominators for each group. The corresponding author was contacted and provided denominator data for the children's age groups, 0 to 2 years; 3 to 4 years and 5 to 14 years. The total number of children age 0 to 14 years in the study was 133.

Self-completion questionnaires were circulated to all residents (380) in April 2002; parents completed the forms on behalf of their children. The rate of chronic conditions in the population was 18% below the threshold of 25% which would warrant exclusion from this review. The response rate to the questionnaire was 92% (350). The questions included place and time of vaccination, any chronic illness, flu-like symptoms, onset of illness and other categories. Visitors from USA, Australia and elsewhere were included in the community. Most people worked or studied in community with exception of teenagers but 77% of the residents spent at least one day per week outside the community. Three hundred and twenty-nine of the 350 residents had been vaccinated, 309 of these in UK and the others in USA. The age structure of those vaccinated outside UK was similar to age structure in UK and all participants were vaccinated between 17 October and 7 November 2001. The inactivated vaccine used for 2001 to 2002 contained strains A/Moscow/10/99-like (H3N2), A/New Caledonia/20/99-like (H1N1) and B/Sichuan/379/99-like. Three of the four batches of vaccine used in USA were of the same type and manufacturer as those used in UK.

The community was subject to an outbreak of influenza A (H3N2) between 10 March and 2 April 2002, with 151 cases of illness peaking on 20 March. There were no reports of increase in ILI in the local population outside the community, which experienced a quiet influenza season, with rates of illness of < 50 new episodes per 100,000 population per week. The influenza A (H3N2) circulating in England was well matched to strain A/Panama/2007/99 included in the vaccine.

Cases of influenza were defined as self-reported fever or chills accompanied by at least one of the following symptoms; cough, sore throat, headache. Laboratory confirmation of influenza using Polymerase Chain Reaction (PCR) was carried out only from blood samples collected from 39 adults, therefore, we have classified the study outcome for children as influenza-like illness. The highest attack rates were found in children under five years. No participants were admitted to hospital. The authors concluded that influenza vaccination in UK was not effective in preventing influenza as defined by study's case definition, although vaccination elsewhere (USA) showed protection against being a case, but this could be chance finding owing to small number of people vaccinated in USA. The authors suggest it is possible that the subunit vaccine used is not as immunogenic in young children than older ones; that participants may have had limited exposure to

circulating wild-type viruses and point out that immunity may have waned given that vaccination using a sub-unit vaccine was carried out six months prior to the influenza outbreak. The data from this study was not included in the meta-analysis of vaccine effectiveness in cohort studies as the group was not representative of the UK population of healthy children, however, the effectiveness data is presented separately in Table 17.
This study was not included in the analysis of effectiveness but is presented in additional Table 1.

Table 1. 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 representative of local population	Cohort	Inactive, trivalent	0-2 years	ILI	11	18	3	5
Nicholls 2004	Cohort from community not representative of local population	Cohort	Inactive, trivalent	3-4 years	ILI	10	16	0	0
Nicholls 2004	Cohort from community not representative of local population	Cohort	Inactive, trivalent	5-14 years	ILI	39	91	0	3
Slepushkin 1974	Intraepidemic study of orally administered vaccine as emergency prophylaxis	RCT	Live (oral) H2N2+B	1-3 yrs	Influenza or ARI >= 10 days after vaccination	187	508	271	492

Table 1. Efficacy and effectiveness data from intraepidemic and non-typical studies (*Continued*)

Ritzwoller 2005	Intraepidemic study	Cohort	Inactive, trivaelent	6-23 months	Influenza-like illness	65	1129	124	1615
Aksenov 1971	Intraepidemic study	Cohort	Live, H2N2 +B, 3 doses 5 days apart	4-7 years	Morbidity due to influenza and ARI	107	760	164	594
Aksenov 1971	Intraepidemic study	Cohort	Live, H2N2 +B, 3 doses 8-10 days apart	4-7 years	Morbidity due to influenza and ARI	81	728	193	674
Aksenov 1971	Intraepidemic study	Cohort	Live, H2N2 +B, 3 doses 5 days apart	7-15 years	Morbidity due to influenza and ARI	143	1358	114	776

Obrosova-Serova 1990

This paper describes a randomised trial of live cold-adapted influenza B vaccine in 196 children carried out in Russia from March to May 1987. The study was carried out in a nursery and boarding school; 64 children aged 3 to 7 years and 132 aged 8 to 15 years were enrolled. The vaccine was cold-adapted LEN-B/14/5/1, a reassortant produced from Leningrad/14/55 and wild-type B/Ann Arbor/1/86. The concentration of virus was 10^7 infective units per dose but this was diluted 1:2 with distilled water prior to inoculation. Children aged 8 to 15 years were immunised one week prior to children aged 3 to 7 years when it was evident no significant illness occurred in older group. In the 3 to 7 years age group, 34 children received vaccine and 30 received placebo, in the 8 to 15 years age group 75 children received vaccine and 57 received placebo. Participants were scheduled to receive two doses of vaccine three weeks apart although 25 vaccine recipients and 18 placebo recipients did not receive their second dose. The vaccine and placebo, distilled water, were administered intranasally in a dose of 0.5 ml using a Smirnoff aerosol sprayer. All participants were observed for four days after vaccination, temperature was measured once a day and children interviewed about subjective complaints. Children with complaints or increased temperature were examined by a paediatrician blinded to whether the child had received vaccine or placebo. Children absent from school were visited at home to ascertain the reason for absence and were examined if ill. The outcomes recorded were fever, defined as axillary temperature above 37.5 ^{o}C and upper respiratory symptoms of coryza and or pharyngitis. The authors concluded that the vaccine was highly attenuated and probably of adequate immunogenicity for kindergarten children but that it may be over attenuated for use in school children.

This study was included in table of safety data.

Principi 2003

This paper describes a prospective RCT carried out in Italy to investigate the socioeconomic impact of inactivated influenza vaccine. The study was conducted in 303 healthy children aged six months to five years and their family contacts during the 2001 to 2002 season. Two hundred and two children were randomised to receive one intramuscular dose of commercial vaccine Inflexal

V (Berna Biotech) and 101 children randomised to receive no vaccination. The strains of influenza included in the vaccine were not specified in the paper. Households were contacted once every two weeks for information on respiratory illnesses and related morbidity among study participants and household contacts and questionnaires were completed during monthly medical visits by trained investigators. The length and definition of the influenza season were not given. The outcomes presented are upper respiratory tract infections; lower respiratory tract infections; febrile respiratory illnesses (no definitions were given for these outcomes); hospital stays; antibiotic prescriptions; antipyretic prescriptions and missed school days. Children who received the vaccine had significantly ($P < 0.005$) fewer respiratory infections, antibiotic and antipyretic prescriptions and missed school days than children in the unvaccinated control group. In a parallel cohort study of children reporting to emergency departments or primary care with a respiratory tract infection, influenza viruses were isolated in 352 of 3771 (9.3%) of children and consisted of 15% A (H1N1), 37% A (H3N2) and 48% influenza B, however, none of the strains were identified.

This study was included in the analysis of vaccine effectiveness, but only in the socio-economic impact comparison.

Rudenko 1988

This paper was translated from Russian and describes an RCT of the efficacy, immunogenicity and safety of a live influenza A (H1N1) vaccine carried out in Russia during the winter 1984 to 1985. The study was carried out in 10,970 children aged 3 to 15 years, of which 3445 were in the 3 to 6 years age group and 7526 in the 7 to 15 years age group. The strain used in the vaccine was not stated in the paper. Classes or groups were randomised to receive two doses of either the vaccine or placebo administered intranasally 28 to 30 days apart using a Smirnov sprayer. In the three to six years group, 1722 children received the vaccine of which 498 received only one dose; 1723 were given the placebo of which 532 only received one dose. In the 7 to 15 years age group, 3687 children received the vaccine, of which 1088 only received one dose of the vaccine; 3838 were given the placebo of which 1050 only received one dose. Follow up was carried out for a six month period after the first vaccination, that is to say, from November 1984 to April 1985. The primary outcome of the study was morbidity due to influenza or ARI during the epidemic period of 28 January to 3 March 1985, the peak of which was recorded between 11 and 17 February. The epidemic period was defined by analysis of morbidity due to influenza and ARI in the adult and child population of the study area, Kaliningrad. The epidemic was described as being of a moderate nature and was caused by an unspecified strain of influenza A (H3N2); only influenza A (H1N1) was included in the vaccine. The lack of match between the vaccine and circulating strain was confirmed by the lack of statistically significant differences in morbidity between the vaccine and placebo groups. To evaluate vaccine safety, morbidity due to illnesses other than influenza and ARI was recorded during the six month follow up period.

Reactions to the first dose of the vaccine were studied in a subgroup of 596 children which consisted of 130 children aged 3 to 6 years and 166 aged 7 to 15 years who had received the vaccine and 132 children aged 3 to 6 years and 168 children aged 7 to 15 years who had received the placebo. The children in the groups were clinically examined for seven working days following inoculation to determine vaccine safety, the temperature outcomes presented are weak reactions (up to 37.3 ^{o}C) and moderate and severe reactions (neither which is defined). Haematological and biochemical tests and analysis of urine were carried out before vaccination, three days after and one month after each dose to evaluate vaccine safety but no data is presented. Morbidity due to illnesses other than influenza or acute respiratory illness within six months of vaccination is also included as an outcome. The measurement of serum antibody levels was carried out but is not included in this review. Temperature sensitivity of vaccine re-isolates and genetic stability of the vaccine were also measured but no data was presented.

The authors found there were no statistical differences in weak temperature reactions between vaccine and placebo sub-groups and no reliable differences between vaccine and placebo group in development of catarrh in nasopharynx and 'symptoms of intoxication'. For the safety outcomes for which no data was presented, the authors state that there was no statistical difference in C-reactive protein between the vaccine and placebo group and no change in blood serum levels of urea, neuraminic acid and transaminase alanine-aminotransferase from which the authors conclude that the vaccine had no harmful effects on the liver and kidneys. Traces of protein and single leucocytes were found in urine in isolated cases in vaccinated and placebo groups, but levels returned to normal after subsequent tests. The authors conclude from the results of the haematology and biochemistry that the vaccine does not have a harmful effect on children aged three to six years but that a wider investigation should be undertaken to confirm this. The frequency, intensity and duration of the clinical reactions indicated that the vaccine was only weakly reactogenicity. No difference in somatic and infectious morbidity of children (excluding acute respiratory infections) were observed over the 6 month observation period, also providing evidence of the vaccine's safety. The authors comment that it was not possible to determine the efficacy of the vaccine because the vaccine and circulating strains did not match.

This study was included in the analysis of effectiveness.

This study was included in table of safety data.

Rudenko 1991

This paper was translated from Russian and describes an RCT of two live recombinant vaccines, A (H1N1) and B administered separately and together. The study was carried out in Cuba in

1006 children aged 3 to 14 years; the year it was carried out is not specified. The influenza A vaccine was a commercial preparation containing strain A/Taiwan/1/87 (H1N1) with biological activity of 7.0 IU of EIE_{50}/0.2 ml (EIE = Experimental Immunogenic Effect in 50% experimental participants). The influenza B vaccine contained strain B/14/5/1 produced by recombination of epidemic strain B/Ann Arbor/2/86 and an attenuated donor strain B/Leningrad/14/17. The activity of B/14/5/1 was 7.0 IU of EIE_{50} in 0.2 ml. The participants were randomised to receive either A, B, A and B together or placebo (distilled water). Of the children enrolled, 486 are missing from the analysis and reasons for the losses to follow up are not given. Of the children aged 3 to 6 years included in the analysis, 53 received influenza A vaccine, 44 influenza B vaccine, 48 both vaccines and 54 placebo. In the 7 to 14 years age group, 70 received influenza A vaccine, 89 influenza B vaccine, 86 both and 76 placebo. Participants received two 0.5 ml doses administered 21 days apart using a Smirnov sprayer. The children were followed up for five days after each dose. The safety outcomes recorded were mild fever (37.1 to 37.5°C), moderate fever (unspecified temperature), malaise, headache, rhinorrhoea, nasal stuffiness, cough, hoarse voice, sore throat, nasal bleeding and conjunctivitis. The other outcomes presented, which are not included in this review, were seroconversion, mean antibody titres and increase in ELISA titre.

Moderate fever was observed in only four vaccine recipients and two placebo recipients and there were no differences in symptoms between preschool and school children for all the safety outcomes presented. The authors state the trial of compatibility between influenza A (H1N1) and B viruses did not reveal additional reactions when using bivalent vaccine.

This study was included in table of safety data.

Rudenko 1993a

This paper describes a multi-centre RCT carried out in Russia over two winters from 1989 to 1991 in 12,837 children aged 7 to 14 years. Children from 34 schools participated in the trial and treatments were assigned randomly to schools rather than individuals. During year one of the study, bivalent inactivated influenza A vaccines were administered containing 3 to 8 μg hemagglutinin of both strains A/Sichuan/2/87-like (H3N2), A/Taiwan/1/86-like (H1N1). In year two trivalent vaccines were used containing A/Shanghai/11/87-like (H3N2), A/Taiwan/1/86-like (H1N1), B/Victoria/2/87-like strains with at least 6.26 $\log_{10}$ median EID_{50} / 0.2 ml dose for each strain. The live vaccines were reassortants derived from A/Leningrad/134/47/57 (H2N2) and B/USSR/60/69 cold adapted donor strains. For each year the wild type parent strains were the same as those in the inactivated vaccines. The inactive vaccine for use in children aged 7 to 10 was chromatographically purified and analysis by US FDA found it to have 'acceptable amounts of free formaldehyde but variable amounts of endotoxin.' The inactivated vaccine was injected subcutaneously in year one and intramuscularly in year two. The placebo used was allantoic fluid, however, only intranasal placebo was included in the second year of the study. The main vaccination programme was begun in mid-October each year. In the first year, the numbers who received live, inactivated and placebo were 4693, 3976 and 2331 respectively. In the second year 4870, 4402 and 6201 received live vaccine, inactivated vaccine and placebo respectively. A subgroup each year was monitored for seven days after inoculation for reactions to the vaccine. One case of low-grade fever (< 38.5 ^{o}C) was observed in the live vaccine group (162 children) in year one. In the second year low-grade fever was observed in 2 of 323 live recipients, 2 of 278 placebo recipients and 13 of 706 in the inactivated vaccine group. In the second year 3.9% of participants who received inactivated vaccine developed induration which was not observed in the first year.

Data on influenza-like illness was collected by nurses in participating schools by examining medical certificates after children had been absent. Any illness diagnosed as respiratory illness or influenza was considered a case. The presence of one or more cases in a child was counted as one outcome. From mid-October in each year nurses in schools monitored illness recorded as acute respiratory disease on medical certificates; when disease started to increase surveillance for viruses was started and specimens collected from at least five children per week to identify influenza viruses. The epidemic period each year was determined by virus isolation, serology and epidemic curves. The epidemic periods were 1 January to 4 March 1990 (9 weeks, the first virus isolated was obtained from a sample taken on 15 January and the last on 22 February) and 14 January to 24 March 1991 (11 weeks). The epidemic in 1989 to 90 was caused by A/Shanghai/11/87-like (H3N2) which is related to, and could not be distinguished from, the strain A/Sichuan/2/87-like contained in the vaccine. In 1990 to 91 the circulating strains were A/Taiwan/1/86-like (H1N1), B/Yamagata/16/88-like and B/Victoria/2/87-like.

In year one, the effectiveness of the live vaccine at preventing influenza-like illness was 30% for children aged 7 to 10 years and 51.9% for children 11 to 14 years. For the inactivated vaccine, effectiveness was 24.2% and 29.6% for each age group respectively. For the second year the live vaccine effectiveness was 39.5% and 21.7% in the 7 to 10 years and 11 to 14 years groups. The effectiveness of the inactivated vaccine was presented as 27.2% (7 to 10 years) and 21.1% (10 to 14 years), however, these were calculated using intranasal placebo data as no corresponding intramuscular placebo was administered in the second winter. The authors concluded that where significant differences were found the live vaccine offered more protection than the inactivated vaccine.

This paper was included in analysis of effectiveness.

This paper was included in the table of safety data.

Rudenko 1996a

Rudenko 1996 describes RCTs of four live vaccines which took place in Russia, Kazakhstan and Cuba between 1986 and 1992. Because of the numbers of studies involved this is a confusing paper to read; 131,930 children aged 3 to 14 years from schools and kindergartens were enrolled in the study. Participants were randomly assigned to groups to receive two 0.5 ml doses of either live vaccine or placebo 21 to 28 days apart.

In the first year of the study (1986 to 1987), 5409 children in Russian were given live vaccine containing strain A/Taiwan/1/86 (H1N1) and 5559 received placebo. In 1986 to 1987 in the Kazakhstan study 32,095 children received vaccine containing strains A/Brazil/1/79 (H1N1) and A/Philippines/1/83 (H3N2) and 24,885 received placebo. In 1988 to 1989, 29,690 received vaccine containing the same strains as 1986 and 31,869 received placebo. Four reassortant live vaccines were tested in Cuba in 1990 to 1991. Seven hundred and seventy-six children received vaccine containing A/Taiwan/1/86 (H1N1); 749 received vaccine containing A/Zakarpartie/354/89 (H3N2) [or A/Shanghai/1/89]; 714 received vaccine containing B/USSR/3/87 [or B/Victoria/3/87]; 755 received vaccine containing A/Taiwan/1/86 (H1N1), A/Zakarpartie/354/89 (H3N2) [or A/Shanghai/1/89] and B/USSR/3/87 [or B/Victoria/3/87] and 669 received placebo. Physiological solution was used as the placebo in all studies. The main outcome was vaccine effectiveness in each part of the study. Other outcomes measured were frequency of febrile reactions within seven days of vaccination and the incidence of 13 somatic and infectious diseases occurring up to 6 months after immunisation. Seroconversion was also a study outcome but is not included in this review.

All children in the Kazakhstan and Cuba studies were included in the trial of vaccine efficacy. From mid-October in each study season, nurses in participating schools started to record details of acute respiratory disease on medical certificates using a series of specific (but not described) diagnoses. When acute respiratory disease incidence began to rise, surveillance for influenza viruses was started using pre and post-illness blood samples and nasal swabs.

In Alma-Ata, Kazakhstan, there was an outbreak of A/Taiwan/1/86 (H1N1), a strain not included in the vaccine, from 17 November to 21 December 1986. The incidence of disease was 24% in children aged 3 to 6 who received vaccine and 33.9% in those that had received placebo. The prophylactic efficacy index for the vaccine was 1.41 (lower limit 1.04), the same efficacy index was found for children aged 7 to 14 years. In 1988 to 1989 there was another outbreak of A/Taiwan/1/86 (H1N1) and B/Victoria/1/87 (neither in vaccine). The epidemic started on 26 March 1989 and lasted for nine weeks. In Havana, Cuba 1990 to 91 episodes of acute respiratory disease occurred in January and February 1991(H3N2, H1N1), May and June 1991 and September to December 1991 (maximum during October and November). Serological records showed that the incidence of both influenza A serotypes (H3N2 and H1N1) were similar, except for July to September when there was more H3N2 virus present than H1N1. The index of efficacy of the vaccine in 1988 to 1989 was 1.6 for both age groups, during this winter circulating viruses were A/Taiwan/1/86 (H1N1) and B/Victoria/1/87. The vaccine did not contain an influenza B strain but the authors conclude that good rates of protection were achieved. Efficacy data was collected during the entire follow up periods not just the weeks of the epidemics.

Participants in the Cuban study were inoculated in November 1990 and monitored for 13 months from 1 December 1990 to 31 December 1991. During that time there were three episodes of acute respiratory disease with circulating strains of influenza A (H1N1) and A (H3N2). Some children experienced several episodes of illness. In the placebo group the total incidence of influenza and acute respiratory disease was 49.5%; for A (H1N1) vaccine - 34.2%; for the A (H3N2) vaccine 32%; B vaccine 28.3% and for the trivalent vaccine - 31.5%. The authors concluded that all four vaccines were effective either when used separately or in combination.

Sub-groups of children were examined each day for seven days following inoculation. Examination of the skin and nasopharynx were carried out and temperature recorded. Although data for febrile reactions among children who received vaccine in three successive years is presented it is unclear from which trial it originated, most likely from the Kazak study although according to the effectiveness data inoculation was carried out only in winters 1986 to 1987 and 1988 to 1989. The authors state in the text that the incidence of upper respiratory tract, catarrhal and systemic reactions was no greater among children vaccinated for three successive years compared with children who were only vaccinated once. Sub-groups of children were also examined for somatic and infectious diseases for six months after inoculation over two years of vaccination. There were no significant differences in the incidence of disease between the vaccinated and placebo groups. Again it is not clear from which study the data are taken although it is most likely to be the Kazakhstan study.

This study was included in the analysis of effectiveness.

This study was included in the table of safety data.

The study is linked to Rudenko 1996b and Grigor'eva 1994.

Grigor'eva 1994

This paper was translated from Russian and describes a study carried out in Cuba from 1990 to 1991 to determine the efficacy and immunogenic properties of a live recombinant trivalent influenza vaccine and three separate recombinant monovalent influenza vaccines, A (H1N1), A (H3N2) and B. The efficacy data for this study is reported is reported in Rudenko 1996a. Grigor'eva 1994 also includes safety outcome data for children aged 5 to 14 years in Havana which is not included in the Rudenko paper. A total of 3663 children aged 5 to 14 participated in the study and were formed

into five groups, three receiving the monovalent vaccine, one the trivalent vaccine and one placebo group (receiving salt solution); the paper does not state the method of allocation. The monovalent vaccines contained the following influenza strains: 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. The trivalent vaccine contained all of the above strains. Safety sub-groups were formed for each arm of the study containing the following numbers of participants: 128, 125, 128, 135 and 98 respectively. Participants were followed up by clinical examination for four days after inoculation to record temperature (in three categories 37.0 to 37.5 ^{o}C; 37.6 to 38.5 ^{o}C; 38.6 ^{o}C or more) and received a medical examination. Serum antibody levels were also included as an outcome but are not included in this review. The authors state that analysis of the reactogenicity did not reveal any pronounced clinical reactions to the vaccines. A temperature of up to 38.5 ^{o}C was recorded for only one child inoculated with the A (HINI) vaccine and for one child inoculated with the B vaccine. Observations were made on the development of other symptoms which could be characteristic of a vaccination reaction: general ill-health, headache, dysphonia, reddening of the throat, nasal bleeding, conjunctivitis and cough and no significant differences were found between the vaccine groups or between inoculated children and those that received placebo.

This study was included the table of safety data.

This study is linked to Rudenko 1996a.

Rudenko 1996b

Rudenko 1996b was translated from Russian and describes a cluster randomised controlled trial to determine the efficacy of a live recombinant vaccine carried out in Kazakhstan from 1983 to 1985. Children aged 3 to 14 years participated in the study. Schools were classified by typological characteristics then randomised to receive either vaccine or placebo or no treatment. The vaccine used was a live recombinant preparation made from two mono vaccines manufactured by the Odessa Production Company containing strains A/47/25/1 (H1N1) and A/47/F (H3N2). Biological activity was 6.0 EID_{50} per 0.2 ml. Both vaccines were blended immediately before administration in a 1:2 ratio and administered using a Smirnov sprayer, two doses of vaccine were administered with an interval of 21 to 28 days. Two cohorts were set up; in the first 25,117 children received live vaccine and 28,703 no treatment; in the second, set up in a different area of the city, 6978 received vaccine and 6182 no treatment and these groups were monitored for incidence of somatic illnesses (excluding influenza and acute respiratory illnesses) for 6 months following vaccination. Results from the first cohort are also presented in Rudenko 1996a.

Children in both cohorts were monitored post vaccination for illness until the end of the influenza season on 5 April 1987. The peak in the influenza epidemic was observed between 17 November 1986 and 21 December 1986. The prophylactic efficacy of the vaccine was assessed by dividing the percentage of cases of influenza and acute respiratory illnesses in the control group by the percentage in the vaccinated group to give an index of efficacy (IE). Indeces of efficacy of 1.41 (large cohort) and 1.42 (small cohort) were found in children aged 3 to 6 years and 1.4 (large) and 1.3 (small) for children aged 7 to 14 years during the epidemic period in November and December 1986. Data was collected during the whole of the follow up periods (not only epidemic periods) and for 1986 to 1987 this included the vaccination period (06 October to 16 November 1986), the rise in the number of cases (from 17 November to 21 December 1986) and the post-epidemic period (22 December 1986 to 05 April 1987).

In the vaccinated safety group there were significantly ($P < 0.01$) fewer cases of ear, nose and throat diseases (excluding tonsillitis and allergies which were separate outcomes) in the control group than the vaccinated group. For other all other outcomes assessed, there were no significant differences.

This study was included in the analysis of effectiveness.

This study was included in the table of safety data.

The study is linked to Rudenko 1996a.

Slepushkin 1974

This paper, translated from Russian, describes a placebo-controlled trial conducted in 1970 to 1971 to test the efficacy of an orally administered live vaccine as emergency prophylaxis in 1000 preschool and school children in USSR. Two studies are reported in the paper. In the first, carried out in 1970, emergency prophylaxis was carried out at the beginning of the epidemic period (dates not specified) in children aged one to three years. Children were randomised into three groups to receive either vaccine, placebo or no treatment. The vaccine contained influenza viruses A2/Istra/10/69 and B/Liks/59 at a concentration of $10^{5.5}$ infectious units per dose. Medium 199 was used as the placebo. Two to three doses were administered with an interval of 10 to 15 days between doses. Contraction of ARI was measured from 10 days after completion of the inoculations. Efficacy data was collected from children who fell ill during the epidemic period. The circulating strains of influenza virus were not specified. Reactions to the vaccine were recorded but the number of days follow up after inoculation was not given.

The objective of the second study, carried out during the peak of an epidemic in January 1971, was to study the efficacy of the vaccine as an interferon inductor, an outcome which is not considered as part of this review. Illness was monitored for only 15 days following inoculation. Pre-school (aged one to three years) children were randomised to receive either oral vaccine or no treatment. Older children, some of whom had been vaccinated the previous year with intranasal live vaccine were put into three groups

(no mention is made of randomisation) the first receiving routine intranasal inoculations, the second - no treatment and the third routine intranasal inoculations and emergency prophylaxis, orally administered three times.

In the first study, 2 of 696 children who received the vaccine experienced a temperature higher than 37.5 ^{o}C after the first dose, compared with 6 out of 798 of the placebo group. After the second dose 4 children from 591 experience a temperature above 37.5 ^{o}C compared with 2 out of 666 in the placebo group. In the first year of the study 36.8% of 508 vaccinated children fell ill during the epidemic compared with 55% of 492 children in the placebo group and 72.5% of 513 children in the no treatment group. The index of vaccine efficacy was 2.0 compared with untreated children and 1.5 compared with those that received placebo. As the objective of the second year study was prophylactic efficacy of the vaccine, illnesses were recorded for the first 15 days following inoculation, however, these data have not been included in any analysis for this review.

This study was not included in the analysis of effectiveness, the data in presented in additional table 17.

This study was included in the table of safety data.

Slepushkin 1988

This paper describes a randomised, single-blinded study of antibody response and safety of live attenuated, cold-adapted recombinant influenza A (H1N1) vaccine. The study was carried out in Russia between September and December 1984; 107 children aged 8 to 11 years from one boarding school participated. The vaccine strain A/47/25/1 (H1N1) was prepared by recombination of a cold-adapted attenuated strain A/Leningrad/134/47/57(H2N2) with wild-type strain A/Leningrad/322/79 (H1N1). The concentration of the vaccine was 10^2 EID_{50}/ml but this was diluted 1:2 with distilled water prior to inoculation. Two 0.5 ml doses were administered to 58 children 28 days apart and 49 children received two doses of placebo, distilled water. Although the vaccine and placebo were coded, there was a difference in colour between the two preparations. Both were administered intranasally using a Smirnoff aerosol sprayer. All participating children were observed for five days after vaccination, their temperature was measured once a day and they were interviewed about subjective complaints. Children with complaints or increased temperature were examined by a paediatrician blinded as to whether the child had received the vaccine or placebo. Children absent from school were visited at home to ascertain the reason for absence and were examined if ill. The safety outcomes presented are fever with a temperature lower than 37.5 ^{o}C, fever with a temperature of 37.5 ^{o}C or higher, headache, sore throat, cough and coryza. Serum antibody levels were determined but are not included in this review. The authors reported that the number of children with reactions after receiving either the vaccine or placebo was low and concluded that the recombinant vaccine was acceptably attenuated for school children.

This study was included in table of safety data.

Slepushkin 1991

This paper was translated from Russian and describes an RCT of the safety and immunogenicity of live recombinant and inactivated influenza A (H3N2) vaccines carried out in Russia during the winter 1987 to 88 in 239 school children aged 8 to 15 years. The live vaccine, produced by the Institute of Experimental Medicine, Leningrad, contained strain A/47/F (H3N2), a recombinant of circulating A/Philippines/2/82 (H3N2) and cold-adapted attenuated A/Leningrad/134/47/57 (H2N2). The vaccine had an infectious titre 7.0 EID_{50}/0.2 ml. The inactivated vaccine was a commercially available (Omutninsk Chemical Factory), chromatographically purified vaccine containing strains similar to A/Philippines/2/82 (H3N2) and A/Chile/1/83 (H1N1) -10 μg hemagglutinin per strain in a 0.5 ml dose. The placebo for the live vaccine was lyophilised allantoic fluid and for inactivated vaccine was salt solution. Sterile salt solution was added in the ratio 1:2 to dilute the live influenza vaccine and allantoic fluid placebo before inoculation. Children of each class were randomly divided into 3 groups; the first group of 97 children received live vaccine (intranasally) and placebo sub-cutaneously; the second group of 56 children received inactivated vaccine (subcutaneously) and placebo intranasally and the third group of 88 children received placebos of both vaccines. Two doses of live vaccine were given 28 days apart, administrated intranasally using a Smirnov sprayer. The inactivated vaccine was administered on the same day as the first dose of live vaccine. The number of days of follow up for this study is not given but the paper states that the study of reactogenicity and immunogenicity was carried out according to previously described methods and cites the following references: Medvedeva 1989; Obrosova-Serova 1990; Slepushkin 1988. In the second study cited children were observed for four days (Obrosova-Serova 1990) and in the third for five days (Slepushkin 1988), it was not possible to find information from the other paper (Medvedeva 1989). For the table of safety outcomes we assumed a follow up period of five days. The following outcomes were measured: temperature (37.1 to 37.5 ^{o}C and 37.6 ^{o}C or above); local reactions (25 mm and below, 26 to 50 mm, above 50 mm); headache; sore throat; cough; head cold and seroconversion (which is not included in this review). Blood samples were taken before vaccination and 25 days after vaccination and tested for inhibition of haemagglutination, microneutralisation and immunogenicity studies (IgG), the results of which are not included in this review. The authors report that both vaccines were well tolerated; no serious general or local reactions were observed. Minor reactions were recorded at the site of injection of the inactivated vaccine, but these did not last more than one to two days.

This study was included in the table of safety data.

Slepushkin 1994

This paper was translated from Russian and is a study comparing

the reactogenicity and immunogenicity of live bivalent or trivalent vaccines and inactivated bivalent and trivalent vaccine in 1817 children in three cohorts between 1989 and 1991. The study was carried out in Russia in children aged between 7 and 14 years. Treatments were assigned to schools, not individuals so we have classified this as a cohort study. In 1989, commercially available Soviet bivalent influenza A vaccines were tested containing the following strains: A/Sichuan/2/87-like (H3N2) and A/Taiwan/1/86-like (H1N1). Seventy-six children received one dose of inactivated vaccine sub-cutaneously; 162 received 2 doses of live vaccine administered intranasally, 3 to 4 weeks apart, using an RDZH-M4 sprayer and 272 received placebo of salt solution (sub-cutaneous) or allantoic fluid (intranasal). The volume of each dose was not specified for either the vaccines or placebo. The inactivated vaccine administered to 7 to 10 year olds contained between 7.5 to 12 μg per dose and for 11 to 14 year olds contained 12.5 μg per dose. The live vaccine contained at least 6.25 CCA/0.2 ml. In 1990, trivalent vaccines were tested containing the following strains: A/Shanghai/11/87 (H3N2), A/Taiwan/1/86 (H1N1) and B/Victoria/2/87. Two-hundred and seventy-one children age 7 to 10 years received inactivated vaccine administered intramuscularly (7.5 to 12 μg hemagglutinin per dose); 435 children aged 11 to 14 years also received inactivated vaccine (23 to 33 μg per dose) by administered sub-cutaneously; 323 children received live vaccine (at least 6.25 CCA/0.2 ml) and 278 received one or other placebo. In 1991, there is no placebo data given so the vaccine data for this year has not been considered for the review. Reactions to the vaccines were studied for five days after vaccination. A temperature of 37.5 ^{o}C was considered a weak reaction, from 37.6 to 38.5 ^{o}C a severe reaction.

The authors state that the reactogenicity of live vaccine was low throughout the study as was the reactogenicity of the inactivated bivalent vaccine in 1989. When trivalent vaccine was administered sub-cutaneously 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 to 38.5 ^{o}C) in 1.3% of the participants and moderate local reactions (26 to 50 mm) in 4.4% of the participants. The authors comment that these exceeded the acceptable reactogenicity of the vaccine according to the directions for use.

This study was included in the table of safety data.

Slobodniuk 2002a

This paper describes a cohort study of the effectiveness of a trivalent inactivated vaccine carried in Russia. The study was carried out for three consecutive years from 1998 to 2001 in 212 children aged 8 to 14 years. The participants were inoculated in 1998 and 1999 with 'Fluarix' (Smith Kline Beecham) and in 2000 with 'Grippol' polymer sub-unit vaccine. In the first year of the study 106 children were vaccinated and 106 children acted as controls, the vaccinated children received an unspecified dose of vaccine containing the strains A/Singapore/6/86 (H1N1), A/Beijing/32/9 (H3N2) and B/Panama/45/90. The following year, 96 of these children were vaccinated with the same vaccine and the control group was reduced to 96. In 2000, there were 80 children in the treatment and control groups. The vaccinated children received an unspecified dose of 'Grippol' vaccine and the strains contained in the vaccine were not given. The primary outcome measured was the number of children recorded with influenza or acute respiratory infection (that is to say, all influenza-like illness) during annual epidemics over the following dates: 25 January to 14 March 1999; 10 January to 21 February 2000 and 25 January to 23 February 2001, the definition of the epidemic periods was not stated and the circulating virus strains not specified. The effectiveness of the vaccine was low after the first year but during the second year the morbidity of children in the vaccinated group was half of that observed in the control group, however, the differences between the treated and control groups were not statistically significant. The morbidity during the epidemic period of children vaccinated with 'Grippol' in year 3 was 2.8 times less than morbidity observed in the control group ($P < 0.005$) and in the opinion of the authors was the maximum protection attainable for inactivated vaccines.

This study was included in the analysis of effectiveness.

Steinhoff 1990

This paper describes a randomised double-blind trial of two live vaccines; a cold-adapted recombinant vaccine and an avian-human recombinant vaccine. The study was carried out in USA during 1986 to 1987 with 107 children aged 6 to 48 months who were H3N2 seronegative. Studies of the cold-adapted and avian-human vaccines were carried out separately in a step-wise dose-escalating fashion with doses ranging from 10^3 to 10^7 infective units per dose. Children who received the 10^7 dose were offered another dose of the same vaccine, one to two months after the first dose. In total, 34 children received the cold-adapted vaccine; 38 the avian-human vaccine and 35 received placebo. The main outcomes of the study were isolation of vaccine strain from participants after vaccination and increase in antibody titre which are not considered for this review. Children were monitored for seven days after inoculation for reactions to the vaccines; these included fever (temperature of 38.1 ^{o}C or above), influenza-like illness, upper respiratory tract illness and otitis media. Mild fever and rhinorrhoea were observed frequently in participants from all groups.

This study was included in the table of safety data.

Steinhoff 1991

This papers describes an RCT to determine the safety of live cold-adapted (ca) re-assortment vaccine and avian-human (ah) re-assortment derived from a cross with a strain isolated from a mal-

lard duck. The data for the avian-human strain was not included in the review. The cold-adapted vaccine was a reassortant formed by crossing A/Kawasaki/9/86 (H1N1) with A/Ann Arbor/6/60 (H2N2). The study was carried out in USA in 122 children aged 6 to 48 months old seronegative to A/Kawasaki/9/86 (H1N1). During the period of the study in 1987 to 1988 there were no influenza viruses circulating. The vaccines were initially tested in young adults before continuing with the children's study. Children were randomised to receive first dose of either ah (40 children), ca (39) or placebo (43). The vaccines were administered in a dose-escalating fashion (10-fold) after each dose was shown to be safe until dose of 10^6 $TCID_{50}$ was reached. Each child received one 0.5 ml dose (0.25 ml per nostril). The participants were observed for one to two hours daily for three days before inoculation and for seven to nine days after.

The outcomes assessed were fever (rectal temperature $\leq 38.1^{o}C$ or $\leq 39.4^{o}C$), upper respiratory tract illness (rhinorrhoea, pharyngitis); lower respiratory tract illness (persistent, wheezing or cough) for $\leq$ two consecutive days and otitis media. Isolation and identification (by HAI assay) of virus from vaccine was carried and antibodies in sera and nasal washes or swabs were determined by HAI assay and ELISA. These data were not included in this review. At the higher doses (10^5 and 10^6) significantly more ah recipients developed fever one to two days after vaccination compared with ca vaccine group (P = 0.03) and placebo group (P = 0.02). The authors also noted that the Ah recipients experienced upper respiratory tract illness and otitis media more often than ca or placebo recipients but these differences were not significant.

This study was included in the table of safety data.

Swierkosz 1994

Swierkosz 1994 describes a double-blind RCT of a trivalent live-attenuated cold-adapted recombinant vaccine conducted in USA in children aged 2 to 22 months. The dates of the trial are not stated in the paper, but was sometime between 1988 and 1993. Twenty-two participants were enrolled, 17 were seronegative to all three hemagglutinin types, two were seronegative to H3N2 & B and two were seronegative to H1N1 and B. The vaccine contained the strains A/Kawasaki/9/86 (H1N1), A/Los Angeles/2/87 (H3N2) and B/Yamagata/16/88; 10^6 $TCID_{50}$ of each strain in a 0.5 ml dose. Seventeen children received three 0.5 ml doses of vaccine administered intranasally at days 0, 60 (range 56 to 66) and 120 (range 112 to 168); 5 participants received placebo (vaccine diluent). After each vaccination, clinical observations were recorded daily for 11 days during which time 5 nasopharyngeal swabs were taken to measure viral shedding (not included in this review); serum for antibody determination (also not included) were also taken before and after each inoculation. The safety outcomes recorded were fever (rectal temperature > 38.3 ^{o}C or axillary > 37.2 ^{o}C); cough (two or more episode on two consecutive days); rhinorrhoea (on two consecutive days); otitis media and lower respiratory tract infection (wheezing or pneumonia). There were no significant differences between reactions in vaccine and placebo recipients for any dose. The authors concluded that the vaccine was safe and immunogenic when administered in a three dose regime.

This study was included in the table of safety data.

Vasil'eva 1982

This paper was translated from Russian and describes an RCT of a chromatographically purified inactive influenza A (H3N2) vaccine carried out in 335 children aged 7 to 15 years in the then USSR. The year the study was conducted is not stated in the paper. There was no mention of randomisation in the text so this paper has been classified as a cohort study. The vaccine included strain A/Texas/1/77 (H3N2), with activity 1142 IU of hemagglutinin per ml. Three hundred and thirty-five children participated in the study and administration of a single dose of vaccine was carried out using two methods - parenteral administration using a needleless injector and parenteral administration using a conventional syringe. Children aged 7 to 10 years received 0.1 ml of vaccine and those aged 11 to 15 years received 0.2 ml. Of the younger age group 70 children received vaccine by injector, 43 vaccine by syringe, 44 placebo by injector and 38 placebo by syringe. In the older age group 35 received vaccine by injector, 34 vaccine by syringe, 37 placebo by injector and 33 placebo by syringe. 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 and presented in the paper. Heart rate, blood pressure, white blood cell, platelet and lymphocyte counts; biochemical tests and renal function tests were also carried out but no data are presented. The presence of influenza or upper respiratory tract illnesses within three months of vaccination was also included as an outcome but we considered the efficacy/effectiveness outcome to be too poorly defined to include in the analysis for this review. Mild fever (37.0 to 37.5 ^{o}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 ^{o}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% participants from this subgroup showed moderate reactions (2.6 to 4.9 mm). Seroconversion was included as an outcome in the study but is not included in this review. The authors concluded that the vaccine was clinically safe and the doses administered and that reactions associated with vaccination were rare.

This study was included in the table of safety data as a cohort study.

Vasil'eva 1988a

This paper was translated from Russian and describes an RCT to determine the safety and immunogenicity study of three forms of an inactivated whole-virion bivalent influenza A vaccine. The study was carried out in 1982 to 1983 in the then USSR in children aged 11 to 14 years. The vaccines included strains A/Leningrad/385/80 (H3N2) and A/Kiev/79 (H1N1) containing 7.0 μg of hemagglutinin in what are described as chromatographic, centrifugal and adsorptive forms. The numbers of participants stated in the methods (13,355 in total; 9,962 received vaccine; 3,393 placebo) contradict the data in Table 3 of the paper that shows 4655 received chromatographic vaccine, 6625 centrifugal vaccine, 491 adsorptive vaccine and 3493 placebo giving a total of 15,264. Groups of teenagers and classes of school children were randomised to receive one of the vaccine types or the placebo of sterile sodium chloride solution. A sub-group of 866 children was followed up for 5 days after each dose of vaccine to assess the following outcomes: temperature ($\leq$ 37.5 ^{o}C, 37.6 to 38.5 ^{o}C, > 38.5 ^{o}C), hyperemia ($\leq$ 25 mm, 26 mm to 50 mm) and infiltration of skin ($\leq$ 25 mm, 26 mm to 50 mm). All of the participants were monitored for 6 months for 15 other outcomes including tonsillitis and bronchitis (the two most common). Seroconversion was measured as an outcome but is not included in this review. Data was presented on hospitalisation of participants within 30 days of vaccination (0.1% to 0.3% for vaccine groups and 0.7% for placebo group), but were not specified for each vaccine type so were not extracted. The authors state that there were no significant differences in the frequency of illness recorded for 6 months following immunisation and conclude that they established the safety and low reactogenicity of the vaccine in children aged 11 to 14 years at the dose used.

This study was included in the table of safety data.

Vasil'eva 1988b

This paper was translated from Russian and describes an RCT of the safety of multiple immunisations of a inactivated bivalent influenza A vaccine in 12,643 children aged 11 to 14 years. The study was carried out in Russia between 1984 and 1986. The vaccine used contained strains A/Philippines/82 (H3N2) and A/Kiev/58/79 (H1N1) with 3.5 μg of hemagglutinin per strain contained in a 0.2 ml dose. Classes of school children were randomised to receive the vaccine or placebo in the first year of the study; 8677 children received vaccine and 3966 received placebo administered sub-cutaneously using BI-2 and BI-3 injectors. All participants were followed up for 30 days after inoculation to determine the frequency of requests for urgent medical attention and of hospitalisation. All morbidity data (excluding influenza and ARI) in the 12,643 children participating in the study was collected and analysed for a 6 month period. In year one, sub-groups of 434 vaccine recipients and 336 placebo recipients were monitored to determine and incidences of temperature (weak reaction 37.0 to 37.5 ^{o}C; moderate reaction 37.6 ^{o}C and above); catarrh and local reactions, namely hyperemia and infiltration ($\leq$ 25 mm; $\geq$ 26 mm) and pain at the administration site. Antibody levels were determined in small sub-groups but are not included as part of this review.

Over the course of the study the children were revaccinated up to three times. The numbers receiving 2, 3 and 4 doses of vaccine were: 2420, 1076 and 107 respectively; the corresponding numbers of placebo recipients were: 1243, 474 and 114. The numbers in safety sub-groups of children receiving 2 doses, 2 doses with 2 year interval, 3 doses, 3 doses with two year interval and 4 doses of vaccine were: 133, 145, 183, 95 and 54 respectively. The corresponding numbers of placebo recipients were: 336, 109, 136, 176, 95 and 65.

The safety outcomes presented were increase in temperature, local reactions and intoxication/catarrh in the nasopharynx. The frequency of weak temperature reactions (< 37.5 ^{o}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 increase in number of inoculations with 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. Frequency of hospitalisation, requests for emergency attention and morbidity due to illnesses other than influenza and ARI were presented for each of the four doses. The frequency of hospitalisation and requests for emergency attention were the same for vaccinated children as those who received placebo and there was no rise in this figure as the number of inoculations increased. The authors concluded that the vaccine reactogenicity was low in children aged 11 to 14 years immunised yearly for up to four years.

This study was included in the table of safety data as a cohort study.

Wright 1976a

This paper reports two studies, an RCT conducted in 35 infants aged 12 to 28 months to determine the safety and reactogenicity of monovalent inactivated influenza B vaccine and a non-randomised study carried out on 33 preschool children aged 3 to 6 years in USA. The year of the study is not clearly stated but is either 1973 or 1974. The vaccine 'Zonomune' (Eli Lilly) contained the strain B/Hong Kong/5/72 with at least 250 CCA units per 0.25 ml dose and was administered sub-cutaneously as a single dose. Infants were randomised to receive vaccine or saline control at the time of a routine clinic visit. Sixteen infants received the

vaccine and 10 received the control. Parents completed a written questionnaire recording local and systemic reactions and recorded the child's temperature at 20.00 hours on the day of injection. Serum antibody levels were determined but are not included in this review. Two groups were formed of pre-school children aged three to six years. In one classroom all 18 children received the vaccine and parents reported any adverse reactions to the teacher. In the second classroom, 12 children received vaccine and 4 received placebo, the temperature and local or systemic reactions in each child was recorded by the vaccination team at 24 hours and 48 hours after inoculation. The data from children in both classrooms was combined in the paper. The authors report that none of the pre-school children exhibited any serious local reactions to administration of the vaccine and reactions were limited to erythema or a slight local swelling. The infants also experienced little local reaction, significantly lower ($P < 0.05$, ^{2}) than the older children, although it is noted that local reactions were recorded by mothers in the 12 to 28 months aged group and by the vaccination team in the 3 to 6 years age group. Two children aged 3 to 6 years had fever of at least 38.9°C and two 'felt hot'. Other systemic reactions were mild. Fever of 38.9°C occurred in over half of the infants (12 to 28 months) between 6 to 12 hours after vaccination and temperatures returned to normal by 24 hours The infants experienced significantly more fever of at least 38.9°C ($P < 0.01$, ^{2}) than the pre-school children, although febrile episodes in older children might have been missed because temperature was not measured until 24 hours after inoculation. Two of the 16 vaccinated infants had seizures 6.5 hours after vaccination with temperatures of 39.4 and 40.0 ^{o}C; both seizures lasted under 5 minutes. A lumbar puncture was performed on one of infants and revealed no abnormality. Neither of the children had a previous history of seizures and each had previously experienced temperatures as high as that recorded on the evening of vaccination. One child subsequently had a fever of 39.4 ^{o}C without a further seizure. The authors concluded this influenza B vaccine was unacceptable for administration to children under 3 years old in the 250 CCA dose used in the study.

This study was included in the table of safety data.

Zangwill 2001

This paper describes a randomised trial of three lots of cold adapted live influenza vaccine carried in USA with 500 children aged between 1 and 3 years carried out over the season 1997 to 1998. This study is linked to the efficacy trial reported in Belshe 1998. Participants were randomised to receive one of five inoculations; three consistency groups were given the vaccine containing strains A/Shenzhen/227/95-like (H1N1), A/Wuhan/359/95-like (H3N2) and B/Harbin/7/94-like recommended for 1997 to 1998; one group received vaccine containing A/Texas/36/91-like (H1N1), A/Wuhan/359/95-like (H3N2) and B/Harbin/7/94-like (recommended for the 1996 to 1997 season during which corresponding efficacy trial was conducted, Belshe 1998) and another group received the placebo - allantoic fluid containing sucrose-phosphate-glutamate. One hundred children were randomised into each of the five groups. Each participant received two 0.5 ml doses intranasally approximately 60 days apart. Outcomes relating to serum antibody levels were not considered for this review. Participants were followed up for 10 days after inoculation and following local and systematic reactions recorded after each dose: congestion, runny nose, sore throat, decreased activity, cough, headache, muscle ache, chills, vomiting and irritability. The numbers in each group that did not receive the second dose of vaccine were 6, 4 and 5 children in the three consistency groups, 6 children in the efficacy lot and 5 in the placebo group.

The authors reported that the vaccines were generally well tolerated with runny nose/nasal congestion the most common adverse event reported. After dose one significantly ($P < 0.05$) more children who received vaccine (63 to 68%) reported nasal congestion compared with those who received placebo (49%). After the second dose the number of reported reactions were lower in all groups. The authors reported that no serious vaccine-related events occurred in any child who received the live vaccine.

This study was included in the table of safety data.

This study is linked to Belshe 1998.

For the 2007 update we identified two further placebo controlled trials of trivalent cold adapted live attenuated influenza vaccine (CAIV-T) (Tam 2007; Vesikari 2006a).

Vesikari 2006a is a double blind placebo controlled randomised trial assessing efficacy and safety of intranasal CAIV-T in children. The trial was conducted in Belgium, Finland, UK, Israel, Spain during the period 2 October 2000 to 31 May 2002. Vesikari 2006b reported on data from the second season. Analyses were carried out only for outcomes occurring in periods of viral circulation in the different centre areas. One thousand, six hundred and sixteen healthy children aged 6 up to 35 months attending day care (at least 12 hours weekly) in one of the centres who continued to be healthy during year two, were included in the primary analysis (951 vaccine and 665 placebo recipients). Originally 1784 participants were randomised on a 3:2 basis. There was considerable attrition between the year one intention-to-treat (ITT) population (1059 in the active arm and 725 in the placebo arm) and the year two per protocol (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 aged 12 to 23 months and 844 aged 24 months or more. In year one vaccine antigen-virus match was good, while in year two the match was not so good because of drifted variants and the appearance of two different strains of influenza B vaccine. Outcomes were either influenza AOM or febrile OM, or time off work for parent or guardian, days off paid work, days of day care missed by ill children - at least one visit to ER/

outpatients department because of ILI, at least one prescription for antibiotics because of ILI, days of antibiotic treatment because of ILI or safety outcomes (reactogenicity events): 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 ^{o}C, 38.6 ^{o}C and 40 ^{o}C axillary respectively or 38 ^{o}C, 39.1 ^{o}C and 40 ^{o}C rectally). Harms are reported in a mixture of table and text formats. There were no statistically significant differences in serious harms between treatment groups during the second influenza surveillance period. Six lower respiratory tract illnesses were reported, all among CAIV-T recipients (five cases of pneumonia and one of bronchospasm). Two cases of pneumonia were judged to be possibly, probably, or definitely related to study vaccination. A total of four participants (two CAIV-T recipients and two placebo recipients) were withdrawn from the study because of adverse events (AEs). No deaths occurred during the study period. The study authors conclude that "cold-adapted influenza vaccine-trivalent was well tolerated and effective in preventing culture-confirmed influenza illness in children as young as six months of age who attended day care".

Tam 2007 is a randomised placebo-controlled trial carried out over three seasons in eight centres in Southeast Asia (enrollment 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 (CAIV-T). Starting from 30 September 2000, 3174 children aged from 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 ration of 2:3. The year one PP efficacy population was 2764 participants (1653 CAIV-T and 1111 placebo). In year two, 2947 participants were re-randomised either to a single dose of CAIV-T or placebo from 9 November 2001. The year two PP efficacy population was 2527 participants. Sixty-nine participants from year one were not randomised in year two but were followed up for safety and influenza surveillance throughout year two. Detailed participant flow with reasons for exclusion from PP analysis is reported in web-only supplementary materials. Participants children had evenly mixed genders (46% versus 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, Standard deviation (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. Although vaccine content was planned to be antigenically representative of the WHO recommendations for the Northern Hemisphere for each year, the vaccines in both years were not well matched.

Paired sera were taken from 111 participants at five sites. However "the same subjects did not necessarily participate in the cohort in both years". The authors conclude that "In year one, efficacy of CAIV-T compared with placebo was 72.9% (95% 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 two, 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 44.2 to 77.3%) influenza strains. In year one, fever, runny nose/nasal congestion, decreased activity and appetite, and use of fever medication were more frequent with CAIV-T after dose one. Runny nose/nasal congestion after dose two (year one) and dose three (year two) and use of fever medication after dose three (year two) 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.

We identified four prospective cohort studies assessing the effectiveness of respectively CAIV (King 2006; Wiggs-Stayner 2006), virosomal (Salleras 2006) and trivalent inactivated vaccines (TIV) (Fujieda 2006) and a retrospective cohort study (Allison 2006) assessing effectiveness of an undescribed vaccine or vaccines. One more included study was a prospective single blind cohort study assessing effectiveness of TIV against OM (Ozgur 2006).

Wiggs-Stayner 2006 is a government-funded nurse-led prospective cohort study carried out in Indiana, USA. The study was carried out in four "entitlement 1" schools which appear to have been populated by lower socio-economic 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. The denominators appear to be 741 children in non-vaccinated schools, out of 550 children in schools one and two, 276 were vaccinated and 274 were not eligible for one reason or another.

Cold adapted recombinant spray vaccine (Flumist) in two intranasal doses or no vaccination were administered but no content, degree of matching or surrounding community or viral circulation are described. Effectiveness was based on days enrolled, days present and days absent during the study period (which is not reported). The authors conclude that "the two 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; one 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".

Salleras 2006 is a 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 influenza and its economic consequences in 966 vaccinated children and 985 non-vaccinated controls attending respectively five and six clinics. The unit of selection was clinic enrolment. Children were aged 3 to 14 and age breakdown by exposure, sex and by two year groupings is reported. Vaccine content is not described. Pharyngeal and nasal swabs were sent to laboratory for culture. Follow up was by parents' questionnaire. Follow up is unclear, as there is no mention of how many children were followed up and whether there was attrition. The authors conclude that "Adjusted vaccination effectiveness was 58.6% (95% CI 49.2 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 pediatric practices with one dose of virosomal subunit inactivated influenza vaccine has the potential to considerably reduce the health and social burdens caused by influenza-related illnesses".

King 2006 is a prospective cohort study carried out in 24 public elementary schools in Maryland, Texas and Minnesota and in four (kindergarten to elementary) schools in Washington during 2004 to 2005. The study assessed the effect of a school-based vaccination programme on ILI, school absenteeism and serious harms at 42 days after vaccination. The schools were divided in 11 clusters, seven of which had random selection of the intervention school and the other four 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. Participants were 5840 pupils in intervention schools and 9451 in control schools, mainly whites in both arms (Table 01). However, Table 02 reports 7892 and 14,017 children respectively in vaccinated and unvaccinated schools and relevant adult denominators are 6046 and 11,080. This apparent discrepancy between tables (1 and 2) and text are not explained. The vaccine used is described as live attenuated vaccine (?Medimmune) intranasally given to all children aged five years or more. The paper describes main circulating virus as drifted from the strain in the vaccine (not described). 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.)".

Fujieda 2006 is a prospective cohort study carried out in 54 clinics around Japan during the 2002 to 2003 season. The study assessed the effectiveness of TIV or standard care against ILI ("acute febrile illness"). Two thousand, nine hundred and thirteen children (1512 vaccinees and 1401 non-vaccinees) under six years of age (52% males) took part. The authors described an analysis stratified by age and other potential confounders (which are reported in Table 01). 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. 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. Content of vaccines is reported but producer and degree of matching are not reported. The authors report that the adjusted odds ratio (OR) and its 95% CI were calculated by the proportional odds model using logistic regression with three-level outcome variables (< 38.0/38.0 ^{o}C or 38.9 ^{o}C/> or = 39.0 ^{o}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 below or equalled years, a more pronounced OR (0.67, 95% 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 (0.81 to 4.19) for those less than one year old and 0.99 (0.72 to 1.36) for those 1.0 to 1.9 years of age and 1.07 (0.80 to 1.44) when these two age groups were combined. Thus, among very young children vaccine effectiveness could not be demonstrated.

Allison 2006 is a five practice retrospective cohort study which took place in Colorado during the 2003 to 2004 season assessing the effectiveness of an undescribed vaccine in preventing ILI in 5193 healthy children aged 6 to 21 months. Data were identified from reimbursement registers. The vaccines used are not described. Outcome was a physician's office attendance for: ILI or pneumonia and influenza (P&I) as defined in the International Classification of Diseases, ninth edition (ICD 9). The authors concluded that "a total of 28% of the patients had an ILI office visit, and 5% had a pneumonia/influenza visit. Hazard ratios (HRs) for full vaccinated (FV) versus unvaccinated (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 partially vaccinated (PV) versus UV were 1.0 (95% CI 0.9 to 1.2) and 1.1 (95% CI 0.8 to 1.5). Although two doses of vaccine were 69% effective against ILI office visits and 87% effective against pneumonia/influenza office visits, one dose did not prevent office visits during the 2003 to 2004 influenza season".

Ozgur 2006 is a single blind prospective study carried out during the 2003 to 2004 season in 135 healthy day care children aged 6 to 60 months around Ankara, Turkey. The study aim was to assess the effectiveness of TIV or standard care in preventing AOM and otitis media with effusion (OME). Randomisation was 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 December 2003 to 31 January 2004 on the basis of influenza and RSV isolates in the community. Three other perinfluenza periods are also described. No mention is made of the circulating strains, although content of the vaccine was that recommended by the WHO. 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 unvaccinated 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 a OM (a syndrome) impractical.

We further identified two case-control studies assessing respectively the efficacy and safety of TIV (Anonymous 2005; Goodman 2006)

Anonymous 2005 is a briefly reported case-control study based on the 45 British Columbia (BC) surveillance system sites in which for the 2004 to 2005 sentinel physicians (physicians participating in an influenza surveillance network, who record the number of patients presenting with influenza-like illness each week) were encouraged to take more swabs. Cases were participants who reported to sentinel physicians with acute onset respiratory illness with fever and cough and one 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. Approximately 35% of participants were aged up 19 years of age. Once the specimens were taken, a questionnaire with details of the case was attached. The authors reported 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". One hundred and sixty five out of 219 participants had enough information as required by the study protocol. Of these 134 were from the period of greatest circulation. Forty and seven cases respectively had specimens positive for influenza A and B and only seven overall were aged 19 or younger. The text appears to suggest that matching between vaccine and wild virus antigens was partial. Diagnostic specimens were swabs or nasal washouts on which PCR was used. The authors concluded "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 CIs. The possibility of no protection cannot be ruled out".

Goodman 2006 is an industry-funded case-control study conducted among healthy children of both sexes who were part of a 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 Advisory Committee on Immunization Practices (ACIP) to extend the immunisation to this age group and study data spans two "seasons": 2002 to 2003 and 2003 to 2004. There is no declaration of conflicts of interest of the authors. Cases were healthy children aged 6 to 23 months for one or more days during the TIV administration period enrolled in the HPMG for one day or more during the study period and had one or more diagnostic codes for a HPMG clinic during the study period. Controls were children with same eligibility criteria matched by birth date and gender. Participants were 13,383 children, of which 3697 received vaccination. The intervention assessed was TIV or no vaccination but no description of content or lot is given although the authors reported that this information was available. For the effectiveness one-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. A number of aspecific outcomes (for example, purpura, white blood cell disorders, rheumatic diseases) were defined by physicians reviewing outcomes of interest observed in the exposed population and clustering the diagnosis by ICD categories and then using VSD categories. The authors concluded that "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".

Risk of bias in included studies

Quality assessment

Of the trials included on vaccine efficacy or effectiveness, two scored highly on all dimensions (Grigor'eva 2002; Hoberman 2003a). Nine trials had adequate randomisation (Belshe 1998; Belshe 2000a; Beutner 1979a; Colombo 2001; Hoberman 2003a; Khan 1996; Principi 2003; Rudenko 1996a; Slepushkin 1974). In the remaining five studies, generation of the allocation sequence was not described. Allocation was concealed adequately in six of the placebo-controlled trials (Alexandrova 1986; Colombo

2001; Grigor'eva 2002; Hoberman 2003a; Khan 1996; Rudenko 1996a). Nine trials documented losses to follow up (Belshe 1998; Belshe 2000a; Beutner 1979a; Clover 1991; Colombo 2001; Gruber 1990; Hoberman 2003a; Khan 1996; Rudenko 1996a) and in all of these, sufficient data were reported to enable an intention-to-treat (ITT) analysis.

Of the safety trials, one study (Zangwill 2001) scored highly on all dimensions. Five trials had adequate randomisation (King 1998; Piedra 2002a; Rudenko 1988; Vasil'eva 1988a; Zangwill 2001). In the remaining 16, the method of allocation sequence was not described or was inadequate. Allocation was concealed adequately in three trials (Gutman 1977; Levine 1977; Zangwill 2001).

Three cohort studies were at low risk of bias on the Newcastle-Ottawa quality assessment scale (Kawai 2003; Maeda 2002; Maeda 2004a), five studies were at medium risk of bias (Bashliaeva 1986 and Chumakov 1987; El'shina 2000; Ritzwoller 2005; Slobodniuk 2002a; Vasil'eva 1982), the other studies were of poorer quality. Hirota 1992 was adequately conducted and reported and was assessed at low risk of bias.

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

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 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.

Vesikari 2006a appears to be a well reported study following CONSORT guidelines. Coding was carried out centrally as well as randomisation and assigned by a blinded investigator on the basis of a pre-printed randomisation schedule. Both ITT and PP populations were defined. There are however, numerous discrepancies within the text and between the text, figures and tables. The vaccine was not available until the end of November in year two 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 one to 62 in year two for unexplained reasons. A major unexplained problem is seen in Table 07 (harm events reporting). Two 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" 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 one, year one recipients, and this may explain the high attrition between dose one, year one and single dose, year two (from 1021 to 631). Safety data were not included in the meta-analysis because of likelihood of reporting bias.

In Tam 2007 randomisation and allocation concealment are described very well but inconsistencies in the text (a missing 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 harm. Figure 1 is not fully explained in the text. It shows four groups at year two 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 third year of the study which disappears in the folds of the text. Perusal of reported safety denominators in Table 06 show the usually discrepancies in trials of CAIV-T vaccines - denominators are reported as ranges with the usual (see Vesikari) caption " †n represents the number of subjects with known values". According to the Table 06, 1345 received CAIVT is season two but according to Figure 1 the total should be 1757. There is no mention of the fate of the other children.

Wiggs-Stayner 2006 has poor quality reporting: no season, vaccine content or viral circulation, no outcome definition, no incidence of ILI, or definition of respiratory illness, likely selection bias, unclear conclusions and a mixture of two designs (before and after comparisons mixed with prospective cohort) make this study at high risk of bias. Because of uncertainty over denominators no data were extracted.

In King 2006 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? This must be an aborted trial. Resource utilisation data are not extracted. Data are reported in Table 02 but conversions cannot take place because denominators are uncertain.

In Salleras 2006 systematic differences between hemicohorts ("adjusted with logistic regression") are reported (significantly smaller families and younger children in the non-vaccinated cohort). No attrition was mentioned. 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?At high risk of bias.

Fujieda 2006 lacks a description of matching, very vague 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 these non-random samplings are generalisable, up to 97% of ILIs were not due to influenza.

In Allison 2006 summary estimates are presented as HR and the authors used a Cox proportional Hazards model, so no disaggregated numerators were available. As several versions of denominator totals were reported, the study results are difficult to interpret. Data are reported by influenza (ILI and P&I) and RSV (ILI) seasons. Asymmetrical reporting?Analysed data come from the period 1 November to 31 December 2003, this is the period when influenza A circulated in a prevalent fashion according to hospital isolates. RSV started circulating at the end of December, 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 two peaks of ILI attendances one corresponding with influenza A circulation and the other with RSV circulation ("influenza and RSV seasons").

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 five private pediatric practices in Denver, Colorado from September 1, 2003 through February 29, 2004 (Kempe 2005). In addition, the implausible sharp division between influenza and RSV around New Year's Eve make the study at high risk of bias.

No data can be extracted as (for example) data for the influenza season (1 November 2003 to 31 December 2003), comparing fully vaccinated with unvaccinated is unclear with shifting denominators. One thousand, eight hundred and eighty four fully vaccinated children at 31 December 2003, the date of the "abrupt" end of influenza A circulation. Two hundred and sixty four events in total were recorded but no arm breakdown was reported.

Ozgur 2006 does not have a very detailed report, likely to be a cohort or controlled clinical trial. Confusingly reported outcome data in Table 02. Numerators were extracted from the text.

In Anonymous 2005 attrition, small sample size, recall and performance bias make this a high risk of bias study.

In Goodman 2006 definitions of cases and controls were 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 a 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 were very few data to compare cases and controls. Effectiveness was reported in an extremely synthetic way. Multivariate modelling use was unclear. How can you adjust for the effects of many concurrent vaccines if you do not have a non-exposed window and the safety outcomes are highly unspecific (for example, urticaria)?The study was classified at high risk of bias. Because of uncertainty over numerators and denominators, no data were extracted.

Effects of interventions

Studies retrieved

From the 1206 titles identified by our searches, we selected and retrieved 136 reports of studies possibly fulfilling inclusion criteria. Eighty-five reports were excluded. The most frequent reason for exclusion was lack of independent controls (29 studies) a non-comparative design (15 studies), studies were carried out in adults (14 studies) and only serological outcome were presented (9 studies). Fifty-one studies have been included in the review. Eight included trials (Desheva 2002; Grigor'eva 1994; Grigor'eva 2002; Rudenko 1991; Rudenko 1996b; Slepushkin 1974; Slepushkin 1991; Vasil'eva 1988a), eight included cohort studies (Bashliaeva 1986 and Chumakov 1987; Burtseva 1991; El'shina 2000; Rudenko 1988; Slepushkin 1994; Slobodniuk 2002a; Vasil'eva 1982; Vasil'eva 1988b) and a controlled clinical trial (CCT) (Aksenov 1971) were translated from Russian. All studies published in English to the end of 2004 were considered for the review, studies published in Russian before 1 July 2004 were considered for the review. One study published in Russian (Gendon 2004) was published in the latter half of 2004 and will be included in a future update of this review. Six requests were made to corresponding authors for further refined data (split by age) and two authors provided the data requested.

For the 2007 update we identified 1090 possible titles of interest. We retrieved 15 and excluded five: Hambidge 2006; Neuzil 2001; France 2004 because they were non comparative, one (Daubeney 1997) because it had not been carried out in healthy children and one (Gendon 2004a) because it assessed the impact of vaccinating children to prevent influenza in the elderly. We included 10 studies. Two were placebo controlled trials over two seasons of cold adapted live attenuated influenza vaccine (CAIV) (Tam 2007; Vesikari 2006a; Vesikari 2006b), 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 retrospective 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).

Outcome measures

Outcomes were classified as influenza in studies where symptoms of influenza were accompanied by a positive laboratory diagnosis either by isolation of the influenza virus or determined serologically with a rise in antibodies to the influenza virus. The outcome influenza-like illness included studies where influenza or influenza-like symptoms only were reported.

Quantitative data synthesis

Eight specific comparisons were constructed for meta-analysis: four included evidence from RCTs (comparisons 01,02, 05, 06), one included the case-control study (comparison 07) and two included evidence from cohort studies (comparisons 03 and 04). Comparisons 01 and 05 included evidence from live attenuated vaccines whereas comparisons 02 and 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 (up to two years, up to six years and over six years) and by type of outcome. Comparisons were constructed for the all outcomes for all vaccine types versus placebo (comparison 08) and all vaccine types versus no intervention (comparison 09).
The comparisons with influenza as an outcome (01.01 and 03.01 for live vaccines; 02.01 and 04.01 for inactivated vaccines) therefore summarise the evidence of vaccine efficacy. The comparisons with influenza-like illness as an outcome (01.02 and 03.02 for live vaccines; 02.02 and 04.02 for inactivated vaccines) summarise vaccine effectiveness.
Comparisons 08.03 to 08.08 (for placebo controlled trials) and comparisons 09.03 to 09.08 (for trials with no intervention) 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 or stratification was possible for these outcomes.

Comparisons showing vaccine efficacy

Comparison 01.01 (evidence from RCTs) shows that live attenuated vaccines have 82% overall efficacy (RR 0.18; 0.11 to 0.29), although we could find no usable data for the below two age group. One study on 1632 children aged 15 to 71 months (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 were presented in the discussion section of the paper, but in the absence of an age breakdown, these data could not be included in the meta-analysis.
Comparison 02.01 (evidence from RCTs) shows that inactivated vaccines appear to have lower efficacy (59%) (RR 0.41; 0.29 to 0.59) than live attenuated vaccines, although the difference is not significant. In children aged two or less the vaccines are not significantly more efficacious than placebo (RR 0.55; 0.18 to 1.69) although this observation is based on a single, relatively small study (Hoberman 2003a).
Comparison 03.01 (evidence from cohort studies) shows that live attenuated vaccines are 44% efficacious (RR 0.56; 0.35 to 0.91) although this observation is based a single, small study in children aged over six (Burtseva 1991).
Comparison 04.01 (evidence from cohort studies) shows that inactivated vaccines have 64% (RR 0.36; 0.12 to 1.11) efficacy in the over six years age group, 66% (RR 0.34; 0.13 to 0.89) in children up to six years of age and are no better than placebo in children up to two years of age (RR 0.63; 0.27 to 1.47).

Comparisons showing vaccines' effectiveness

Comparison 01.02 (evidence from RCTs) shows that live attenuated vaccines have 33% overall effectiveness (RR 0.67; 0.62 to 0.72), but we could find no evidence for children aged two years or below.
Comparison 02.02 (evidence from RCTs) shows that inactivated vaccines have 36% overall effectiveness (RR 0.64; 0.54 to 0.76). We could find no evidence for children aged two years or below.
Comparison 03.02 (evidence from cohort studies) shows that live attenuated vaccines are 37% effective in the over five age group (RR 0.63; 0.57 to 0.69).
Comparison 04.02 (evidence from cohort studies) shows that inactivated vaccines have overall 45% effectiveness (RR 0.55; 0.42 to 0.70). We could find no data for children under two years old. There is a lack of effectiveness in children aged up to six (RR 0.81; 0.65 to 1.01) which is just short of significance. However, this must be interpreted with caution because the sizeable decrease in RR since the 2005 of our review is due to the inclusion of a large cohort study at high risk of bias (Fujieda 2006). Inactivated vaccines were more effective, 56% (RR 0.44; 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 (Hirota 1992) (comparison 07.02) 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 odds ratios are reported).
The other case-control study reports no effect of TIV on physician consultations for influenza (OR 0.87; 0.12 to 6.46) in children aged 6 months to 18 years, but the findings may be due to the study's small size (37 observations) (Anonymous 2005).

Evidence on rare outcomes

Comparisons 08.03 to 08.11 and 09.03 to 09.10 assessed evidence from RCTs on rare outcomes. Vaccines were significantly more effective either than placebo in reducing school absence (RR 0.49; 0.26 to 0.92) or than standard care (RR 0.14; 0.07 to 0.27). Both observations are based on single studies (Colombo 2001; Khan 1996). A third trial found a significant decrease in school days missed by vaccinated children (mean difference -4.23, -6.81, -1.65) (Principi 2003). A high risk of bias trial shows a significant effect of CAIV-T against outpatients attendance for pneumonia and influenza (OR 0.60; 0.43 to 0.82) and parents' working days lost (OR 0.62; 0.39 to 1.00) (Vesikari 2006a). The effects on all other outcomes (secondary cases, lower respiratory tract disease, drug prescriptions, AOM 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 (Ozgur 2006), inactivated vaccines do not reduce the risk of AOM (although this may be due to the small denominator of 119). Virosomal vaccines reduce antibiotic consumption (OR 0.77; 0.61 to 0.98), school absenteeism (OR 0.42; 0.34 to 0.51) and work absenteeism (OR 0.69; 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 (Salleras 2006).

Evidence on number of doses

Comparisons between the efficacy of one and two-dose schedules of live attenuated vaccines versus placebo appear to favour the two-dose schedule: 73% effectiveness (RR 0.27; 0.12 to 0.61) (Belshe 1998; Belshe 2000a; Clover 1991; Gruber 1990) compared with 89% efficacy (RR 0.11; 0.04 to 0.26), although this estimate is based on two two-dose studies only (Belshe 1998, 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; 0.03 to 0.49 and RR 0.26; 0.17, 0.60). These observations must be interpreted with caution as they are based on a single cohort study at high risk of bias (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 (Khan 1996).

Additional Table 2 shows the results of the stepwise sensitivity analysis excluding Russian/USSR studies. All comparison except 01.01 and 01.02 (influenza and influenza-like illness in live vaccine trials) were sensitive to the exclusion of evidence from Russian/USSR studies. For comparison 01.02 exclusion of six independent data sets made the effectiveness estimate non-significant in children older than six years but enhanced the total effectiveness from 38% to 67%. For comparison 02.02, effectiveness estimates for children older than six years were not significantly affected but were increased from 28% to 76%. Comparisons 03.01 and 03.02 were depopulated by the removal of the one data set in each group. For comparison 04.01, the non-significant 64% estimate for children older than six years became significant (80%), whereas for comparison 04.02, the estimates for those older than six years (58%) remained significant but increased in size. Inclusion of studies from the 2007 update did not materially alter our findings.

Table 2. Sensitivity analysis

Comparison	Vaccine type	Study type	Outcome	Age group	Without Russian studies	Datasets	All studies	Datasets
					Relative risk (random) [95% CI]		Relative risk (random) [95% CI]	
01.01	Live	RCTs	Influenza	</= 2 years				

Table 2. Sensitivity analysis (*Continued*)

				</= 6 years	0.15 (0.10 - 0.23)	5	0.15 (0.10 - 0.23)	5
				> 6 years	0.47 (0.23 - 0.97)	1	0.47 (0.23 - 0.97)	1
				Total	0.18 (0.11 - 0.29)	6	0.18 (0.11 - 0.29)	6
01.02	Live	RCTs	Influenza-like illness	</= 2 years				
				</= 6 years	0.54 (0.12 - 2.42)*	1	0.67 (0.57 - 0.77)	5
				> 6 years	0.12 (0.01 - 2.11)*	1	0.67 (0.60 - 0.74)	8
				Total	0.39 (0.10 - 1.48)*	2	0.67 (0.62 - 0.72)	13
02.01	Inactivated	RCTs	Influenza	</= 2 years	0.55 (0.18 - 1.69)	2	0.55 (0.18 - 1.69)	2
				</= 6 years	0.61 (0.34 - 1.08)	2	0.61 (0.34 - 1.08)	2
				> 6 years	0.31 (0.22 - 0.45)	3	0.31 (0.22 - 0.45)	3
				Total	0.41 (0.29 - 0.59)	7	0.41 (0.29 - 0.59)	7
02.02	Inactivated	RCTs	Influenza-like illness	</= 2 years				
				</= 6 years	0.39 (0.21 - 0.69)	3	0.39 (0.21 - 0.69)	3
				> 6 years	0.24 (0.08 - 0.70)+	2	0.72 (0.66 - 0.78)	4

Table 2. Sensitivity analysis (*Continued*)

				Total	0.34 (0.24 - 0.50)+	5	0.64 (0.54 - 0.76)	7
03.01	Live	Cohort studies	Influenza	</= 2 years				
				</= 6 years				
				> 6 years			0.56 (0.35 - 0.91)	1
				Total	No studies		0.56 (0.35 - 0.91)	1
03.02	Live	Cohort studies	Influenza-like illness	</= 2 years				
				</= 6 years				
				> 6 years	0.63 (0.57 - 0.69)	1	0.63 (0.57 - 0.69)	2
				Total	0.63 (0.57 - 0.69)	1	0.63 (0.57 - 0.69)	2
04.01	Inactivated	Cohort studies	Influenza	</= 2 years	0.63 (0.27 - 1.47)	3	0.63 (0.27 - 1.47)	3
				</= 6 years	0.34 (0.13 - 0.89)	1	0.34 (0.13 - 0.89)	1
				> 6 years	0.20 (0.10 - 0.39)*	1	0.36 (0.12 - 1.11)	2
				Total	0.36 (0.19 - 0.66)	5	0.42 (0.25 - 0.73)	6
04.02	Inactivated	Cohort studies	Influenza-like illness	</= 2 years				

Table 2. Sensitivity analysis (*Continued*)

				</= 6 years	0.40 (0.13 - 1.20)	3	0.81 (0.65 - 1.01)	4
				> 6 years	0.10 (0.05 - 0.21)+	1	0.44 (0.29 - 0.68)	7
				Total	0.26 (0.07 - 0.92)+	4	0.55 (0.42 - 0.70)	11
*significance change								
+ possible decision-making signficance change								
Comparison 01.01	Live vaccine							

Safety studies

Thirty-two studies met the review inclusion criteria and included safety outcomes. Ten of these studies (Alexandrova 1986; Belshe 1998; Belshe 2000a; Beutner 1979a; El'shina 2000; Grigor'eva 2002; Gruber 1990; Khan 1996; Rudenko 1993a; Rudenko 1996a) were also included in the vaccine efficacy or effectiveness analysis. Two papers present further data from trials of vaccines efficacy or effectiveness; Piedra 2002a presented further safety data from the trial described in Belshe 1990 and 2000; Grigor'eva 1994 (translated from Russian) provides the safety data for the trial described in Rudenko 1996a.

Of the 20 trials safety only trials included in this review, nine were translated from Russian (Desheva 2002; Rudenko 1988; Rudenko 1991; Rudenko 1996b; Slepushkin 1991; Slepushkin 1994; Vasil'eva 1982; Vasil'eva 1988a; Vasil'eva 1988b). Three studies contained efficacy data which was excluded for the following reasons: participants receiving one or two doses could not be separated (Desheva 2002); numbers of participants in each arm and follow up times were not presented (Slepushkin 1994) and numbers of participants were not presented (Vasil'eva 1988a). Of the 32 studies, four included safety outcomes for both live and inactivated vaccines (Gruber 1990; Khan 1996; Slepushkin 1991; Slepushkin 1994), one of these (Slepushkin 1994) was classified as a cohort study as treatments were assigned to schools not to individuals, the others described RCTs. All safety studies were placebo

controlled with one exception where the comparator was no treatment (El'shina 2000).

Twenty-five studies presented data on the safety of live attenuated vaccine in children aged 2 months to 15 years old (Alexandrova 1986; Belshe 1992; Belshe 1998; Belshe 2000a; Beutner 1979a; Desheva 2002; Grigor'eva 1994; Grigor'eva 2002; Gruber 1990; Gruber 1996; Gruber 1997; Khan 1996; King 1998; Obrosova-Serova 1990; Piedra 2002a; Rudenko 1988; Rudenko 1991; Rudenko 1993a; Rudenko 1996a; Slepushkin 1988; Slepushkin 1991; Slepushkin 1994; Steinhoff 1990; Swierkosz 1994; Zangwill 2001), all were RCTs with the exception of Slepushkin 1994. Eleven studies presented safety data for inactivated vaccines in children aged 12 months to 18 years old, seven were RCTs (Gruber 1990; Gutman 1977; Khan 1996; Levine 1977; Slepushkin 1991; Vasil'eva 1988a; Wright 1976a), three were cohort studies (Slepushkin 1994; Vasil'eva 1982; Vasil'eva 1988b) 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). Only one trial, Wright 1976a, which presented data from 35 participants aged 12 to 28 months old, investigated the safety of inactivated vaccines in children younger than three years of age, whereas 10 studies were found on the safety of live attenuated vaccines in children under three years of age.

Three studies from the 2007 update reported safety data; two were CAIV-T placebo controlled trials (Tam 2007; Vesikari 2006a) and one was a case control of the safety of TIV (Goodman 2006). One more cohort study reported safety data in an appendix (King 2006).

The following short-term outcomes were presented in the trials of live attenuated vaccines:

Temperature - 25 RCTs and one cohort study

Nasal symptoms - 15 RCTs, rhinorrhoea and/or nasal congestion was included as an outcome in 11 studies, coryza in two studies and nasal bleeding in one study

Headache - six RCTs

Gastro-intestinal symptoms - four RCTs

Cough - nine RCTs

Sore throat - seven RCTs

Symptoms of influenza or ARI (within seven days of inoculation) - four RCTs

Other respiratory tract symptoms - 14 RCTs

Otitis media - seven RCTs

Conjunctivitis - one RCT

Use of antibiotics, antihistamines and antipyretics - one RCT

Allergic reactions - one RCT

Serious adverse events and vaccine related serious adverse events - one RCT

General symptoms including decreased activity, irritability, malaise, muscle aches - seven RCTs (Table 3).

Table 3. Live vaccine safety, RCTs, outcomes up to 6 months

Study reference	Influenza types	Dose	Age group (years)	Outcome	Follow -up (days)	n treatment	N treatment	n placebo	N placebo
Belshe 1998	A1+A2+B	1&2	15-71 months	Serious adverse events	42	0	1070	0	532
Belshe 1998	A1+A2+B	1&2	15-71 months	Vaccine-related serious adverse events	102	0	1070	0	532
Piedra 2002	A1+A2+B	1	15-71 months	Afebrile illness	11-42	942 §	1070 §	473 §	532 §
Piedra 2002	A1+A2+B	1	15-71 months	Febrile illness	11-42	150 §	1070 §	80 §	532 §
Piedra 2002	A1+A2+B	1	15-71 months	Otitis media	11-42	32 §	1070 §	16 §	532 §
Piedra 2002	A1+A2+B	1	15-71 months	Febrile otitis media	11-42	21 §	1070 §	16 §	532 §

Table 3. Live vaccine safety, RCTs, outcomes up to 6 months (*Continued*)

Piedra 2002	A1+A2+B	1	15-71 months	LRTI	11-42	21 §	1070 §	11 §	532 §
Piedra 2002	A1+A2+B	1	15-71 months	Oral antibiotics	11-42	102	1070	52	532
Piedra 2002	A1+A2+B	1	15-71 months	Analgesic/ antipyretic	11-42	152	1070	86	532
Piedra 2002	A1+A2+B	1	15-71 months	Anthistamine/decongestant/ antitussive	11-42	162	1070	76	532
Piedra 2002	A1+A2+B	1	26-85 months	Afebrile illness	11-42	862 §	917 §	415 §	441 §
Piedra 2002	A1+A2+B	1	26-85 months	Febrile illness	11-42	55 §	917 §	26 §	441 §
Piedra 2002	A1+A2+B	1	26-85 months	Otitis media	11-42	9 §	917 §	9 §	441 §
Piedra 2002	A1+A2+B	1	26-85 months	Febrile otitis media	11-42	18 §	917 §	4 §	441 §
Piedra 2002	A1+A2+B	1	26-85 months	LRTI	11-42	9 §	917 §	9 §	441 §
Piedra 2002	A1+A2+B	1	26-85 months	Oral antibiotics	11-42	53	917	29	441
Piedra 2002	A1+A2+B	1	26-85 months	Analgesic/ antipyretic	11-42	67	917	28	441
Piedra 2002	A1+A2+B	1	26-85 months	Anthistamine/decongestant/ antitussive	11-42	51	917	37	441
Rudenko 1996 II	See footnote	1	3-15	Tonsillitis	6 months	8	1224	20	1191
Rudenko 1996 II	See footnote	1	3-15	Phlegmon (abscess)	6 months	0	1224	1	1191
Rudenko 1996 II	See footnote	1	3-15	Furuncles	6 months	1	1224	1	1191

Table 3. Live vaccine safety, RCTs, outcomes up to 6 months (*Continued*)

Rudenko 1996 II	See footnote	1	3-15	Acute intestinal infections	6 months	4	1224	3	1191
Rudenko 1996 II	See footnote	1	3-15	Heart diseases	6 months	1	1224	0	1191
Rudenko 1996 II	See footnote	1	3-15	Pneumonia	6 months	8	1224	9	1191
Rudenko 1996 II	See footnote	1	3-15	Bronchitis	6 months	49	1224	66	1191
Rudenko 1996 II	See footnote	1	3-15	Allergy	6 months	11	1224	12	1191
Rudenko 1996 II	See footnote	1	3-15	Pharyngitis (laryngitis)	6 months	38	1224	46	1191
Rudenko 1996 II	See footnote	1	3-15	Kidney disease,	6 months	3	1224	1	1191
Rudenko 1996 II	See footnote	1	3-15	Diseases of nervous system,	6 months	1	1224	0	1191
Rudenko 1996 II	See footnote	1	3-15	Conjunctivitis	6 months	6	1224	6	1191
Rudenko 1996 II	See footnote	1	3-15	Other diseases	6 months	12	1224	14	1191
Rudenko 1996 II Yr2	See footnote	2	3-15	Tonsillitis	6 months	1	220	0	195
Rudenko 1996 II Yr2	See footnote	2	3-15	Phlegmon (abscess)	6 months	0	220	0	195
Rudenko 1996 II Yr2	See footnote	2	3-15	Furuncles	6 months	0	220	0	195
Rudenko 1996 II Yr2	See footnote	2	3-15	Acute intestinal infections	6 months	1	220	0	195

Table 3. Live vaccine safety, RCTs, outcomes up to 6 months (*Continued*)

Rudenko 1996 II Yr2	See footnote	2	3-15	Heart diseases	6 months	0	220	0	195
Rudenko 1996 II Yr2	See footnote	2	3-15	Pneumonia	6 months	0	220	0	195
Rudenko 1996 II Yr2	See footnote	2	3-15	Bronchitis	6 months	5	220	6	195
Rudenko 1996 II Yr2	See footnote	2	3-15	Allergy	6 months	2	220	1	195
Rudenko 1996 II Yr2	See footnote	2	3-15	Pharyngitis (laryngitis)	6 months	5	220	4	195
Rudenko 1996 II Yr2	See footnote	2	3-15	Kidney disease,	6 months	2	220	0	195
Rudenko 1996 II Yr2	See footnote	2	3-15	Diseases of nervous system,	6 months	0	220	0	195
Rudenko 1996 II Yr2	See footnote	2	3-15	Conjunctivitis	6 months	2	220	1	195
Rudenko 1996 II Yr2	See footnote	2	3-15	Other diseases	6 months	2	220	16	195
Desheva 2002	A1+A2+B	1	3-6	Infections (exc. influenza & ARI)	6 months	26	182	6	68
Desheva 2002	A1+A2+B	1	3-6	Somatic illnesses	6 months	14	182	5	68
Desheva 2002	A1+A2+B	1	3-6	Allergies	6 months	3	182	2	68
Rudenko 1988	A1	2	3-6	Morbidity (excluding influenza &	6 months	94	1224	109	1191

Table 3. Live vaccine safety, RCTs, outcomes up to 6 months (*Continued*)

				ARI)					
Rudenko 1988	A1	2	7-15	Morbidity (excluding influenza & ARI)	6 months	92	2599	95	2788
Footnote - data is combined for mono-valent A1, A2, B; bivalent A1+A2 and triva-lent vaccine									
§ n = Mean events/ child x N									

Twenty-one of the RCTs of live vaccines safety presented temperature rise as an outcome with a total of 5762 children in the vaccine arms and 2879 children in the placebo arms. One cohort study presented temperature as an outcome (Slepushkin 1994) with 485 children in the vaccine arm and 275 children in the placebo arm. Six RCTs of inactivated vaccine safety (list) presented temperature rise as an outcome with 936 children in the vaccine arms and 796 in the placebo arms; the three cohort studies presenting temperature as an outcome included 1004 children in the vaccine arms and 482 in the placebo arms.

The two RCTs (three data sets) of the 2007 update reported fever as mild, moderate or severe (Tam 2007, Vesikari 2006a; Vesikari 2006b).

The full list of temperature outcomes for trials of live attenuated vaccine is presented in additional tables Table 4 and Table 5. All of the outcomes for short-term nasal reactions are presented in additional Table 6. Sore throat, tonsillitis, cough, headache, conjunctivitis and otitis media are shown in additional Table 7. General reactions and other respiratory symptoms are presented in additional tables Table 8 and Table 9. The full key of symbols used in the tables is at Table 10.

Table 4. Live vaccine safety, RCTs, mild temperature reactions

Study reference	Influenza types	Number of doses	Age group (years)	Temperature	Follow up (days)	n treatment	N treatment	n control	N control
Up to 37.5°C									
Slepushkin 1974 (oral vaccine)	H2N2+B	1	1-3	<= 37.5°C	unknown	9	696	9	798
Slepushkin 1974 (oral vaccine)	H2N2+B	2	1-3	<= 37.5°C	unknown	3	591	1	666
Alexandrova 1986	A1+A2	2	3-6	37-37.5°C	5	2	184	1	83
Rudenko 1996 I Yr 1	A1+A2	1	3-6	37.1°C-37.5°C	7	11	130	11	132
Rudenko 1996 I Yr 2	A1+A2	2	3-6	37.1°C-37.5°C	7	6	39	5	50
Rudenko 1996 I Yr 3	A1+A2	3	3-6	37.1°C-37.5°C	7	7	68	4	61
Rudenko 1991	A1	2	3-6	37.1-37.5°C	5	0	53	0	54
Rudenko 1991	B	2	3-6	37.1-37.5°C	5	1	44	0	54
Rudenko 1991	A1+B	2	3-6	37.1-37.5°C	5	0	48	0	54
Desheva 2002	A1+A2+B	1 or 2	3-6	<= 37.5°C	5	25	184	9	72
Rudenko 1988	A1	2	3-15	<= 37.5°C	7 wd	20	450	27	200
Grigoreva 1994	A1	2	5-14	37.0-37.5°C	4	4	128	3	98
Grigoreva 1994	A2	2	5-14	37.0-37.5°C	4	2	125	3	98

Table 4. Live vaccine safety, RCTs, mild temperature reactions (*Continued*)

Grigoreva 1994	B	2	5-14	37.0-37.5°C	4	1	128	3	98
Grigoreva 1994	A1+A2+B	2	5-14	37.0-37.5°C	4	0	135	3	98
Rudenko 1991	B	2	7-14	37.1-37.5°C	5	0	89	0	76
Rudenko 1996 I Yr 1	A1+A2	1	7-14	37.1°C-37.5°C	7	9	166	16	168
Rudenko 1996 I Yr 2	A1+A2	2	7-14	37.1°C-37.5°C	7	11	70	9	85
Rudenko 1996 I Yr 3	A1+A2	3	7-14	37.1°C-37.5°C	7	7	48	5	49
Rudenko 1991	A1	2	7-14	37.1-37.5°C	5	1	70	0	76
Rudenko 1991	A1+B	2	7-14	37.1-37.5°C	5	0	86	0	76
Alexandrova 1986	A1+A2	2	7-15	37-37.5°C	5	0	100	0	90
Slepushkin 1988	A1	2	8-11	< 37.5°C	5	1	43	1	38
Slepushkin 1991	A2	1	8-15	37.1-37.5°C	? 4/5	1	97	1*	88*
Slepushkin 1991	A2	2	8-15	37.1-37.5°C	? 4/5	4	95	3*	78*
Khan 1996	A1+A2+B	1	9-12	37.0-37.4 °C	4	5	200	1	100

Table 5. Live vaccine safety, RCTs, moderate temperature reactions

Study reference	Influenza types	Number of doses	Age group (years)	Temperature	Follow up (days)	n treatment	N treatment	n control	N control

Table 5. Live vaccine safety, RCTs, moderate temperature reactions (*Continued*)

Under to over 38°C [range 37.6-39.4°C]									
Swierkosz 1994	A1+A2+B	3	2-22 m	>38.3°C rec, >37.2°C ax	11	3	13	0	1
Gruber 1996	A1	1	6-18 m	>= 37.8°C	10	5	44	10	44
Gruber 1996	A2	1	6-18 m	>= 37.8°C	10	13	45	10	44
Gruber 1996	A1+A2	1	6-18 m	>= 37.8°C	10	12	47	10	44
Belshe 1992	A1+A2+B	1	6 m-13 yr	> 38.3°C rec (1), oral > 37.8°C (2)	11	2	32	2	17
Slepuskin 1974 (oral vaccine)	H2N2+B	1	1-3	> 37.5°C	unknown	2	696	6	798
Slepuskin 1974 (oral vaccine)	H2N2+B	2	1-3	> 37.5°C	unknown	4	591	2	666
Zangwill 2001 a	A1+A2+B	1	1-3	>37.8°C	10	19	100	14	100
Zangwill 2001 a	A1+A2+B	2	1-3	>37.8°C	10	11	94	9	95
Zangwill 2001 b	A1+A2+B	1	1-3	>37.8°C	10	17	100	14	100
Zangwill 2001 b	A1+A2+B	2	1-3	>37.8°C	10	12	96	9	95
Zangwill 2001 c	A1+A2+B	1	1-3	>37.8°C	10	16	100	14	100

Table 5. Live vaccine safety, RCTs, moderate temperature reactions (*Continued*)

Zangwill 2001 c	A1+A2+B	2	1-3	>37.8°C	10	10	95	9	95
Zangwill 2001 d	A1+A2+B	1	1-3	>37.8°C	10	26	100	14	100
Zangwill 2001 d	A1+A2+B	2	1-3	>37.8°C	10	7	94	9	95
Belshe 1998	A1+A2+B	1&2	15-71 m	> 37.6°C ax, 37.7°C oral, 38.1°C rec	10	161	1070	39	532
Piedra 2002	A1+A2+B	1	15-71 m	>38.1°C rec, 37.8°C oral, 37.6°C ax	10	174	1070	64	532
Piedra 2002	A1+A2+B	2	15-71 m	>38.1°C rec, 37.8°C oral, 37.6°C ax	10	94	854	45	418
Piedra 2002	A1+A2+B	1	15-71 m	>38.1°C rec, 37.8°C oral, 37.6°C ax	2	76	1070	8	532
Piedra 2002	A1+A2+B	1	15-71 m	>38.1°C rec, 37.8°C oral, 37.6°C ax	3	47	1070	12	532
Piedra 2002	A1+A2+B	1	15-71 m	>38.1°C rec, 37.8°C oral, 37.6°C ax	8	13	1070	8	532
Piedra 2002	A1+A2+B	1	15-71 m	>38.1°C rec, 37.8°C oral, 37.6°C ax	9	16	1070	8	532

Table 5. Live vaccine safety, RCTs, moderate temperature reactions (*Continued*)

Piedra 2002	A1+A2+B	2	15-71 m	>38.1°C rec, 37.8°C oral, 37.6°C ax	2	13	854	5	418
Piedra 2002	A1+A2+B	2	15-71 m	>38.1°C rec, 37.8°C oral, 37.6°C ax	3	21	854	4	418
Piedra 2002	A1+A2+B	2	15-71 m	>38.1°C rec, 37.8°C oral, 37.6°C ax	8	18	854	11	418
Piedra 2002	A1+A2+B	2	15-71 m	>38.1°C rec, 37.8°C oral, 37.6°C ax	9	12	854	10	418
Piedra 2002	A1+A2+B	1	26-85 m	>38.1°C rec, 37.8°C oral, 37.6°C ax	10	18	917	8	441
Piedra 2002	A1+A2+B	1	26-85 m	>38.1°C rec, 37.8°C oral, 37.6°C ax	10	99	917	42	441
Piedra 2002	A1+A2+B	1	26-85 m	>38.1°C rec, 37.8°C oral, 37.6°C ax	2	20	917	8	441
Piedra 2002	A1+A2+B	1	26-85 m	>38.1°C rec, 37.8°C oral, 37.6°C ax	3	18	917	2	441

Table 5. Live vaccine safety, RCTs, moderate temperature reactions (*Continued*)

Piedra 2002	A1+A2+B	1	26-85 m	>38.1°C rec, 37.8°C oral, 37.6°C ax	8	11	917	9	441
Piedra 2002	A1+A2+B	1	26-85 m	>38.1°C rec, 37.8°C oral, 37.6°C ax	9	21	917	13	441
Alexandrova 1986	A1+A2	2	3-6	37.6-38.5°C	5	0	184	1	83
Rudenko 1996 I Yr 1	A1+A2	1	3-6	37.6°C-38.5°C	7	2	130	1	132
Rudenko 1996 I Yr 2	A1+A2	2	3-6	37.6°C-38.5°C	7	0	39	0	50
Rudenko 1996 I Yr 3	A1+A2	3	3-6	37.6°C-38.5°C	7	1	68	1	61
Rudenko 1991	A1	2	3-6	> 37.5°C	5	2	53	1	54
Rudenko 1991	B	2	3-6	> 37.5°C	5	1	44	1	54
Rudenko 1991	A1+B	2	3-6	> 37.5°C	5	0	48	1	54
Desheva 2002	A1+A2+B	1or 2	3-6	37.6-38.5°C	5	0	184	0	72
Rudenko 1988	A1	2	3-6	>37.3°C	7 wd	0	164	0	132
Obrosova-Serova 1990	B	2	3-7	> 37.5°C ax	4	0	26	4	26
Grigoreva 1994	A1	2	5-14	37.6-38.5°C	4	2	128	0	98
Grigoreva 1994	A2	2	5-14	37.6-38.5°C	4	0	125	0	98

Table 5. Live vaccine safety, RCTs, moderate temperature reactions (*Continued*)

Grigoreva 1994	B	2	5-14	37.6-38.5°C	4	0	128	0	98
Grigoreva 1994	A1+A2+B	2	5-14	37.6-38.5°C	4	0	135	0	98
Rudenko 1993	A1+A2	2	7-14	<38.5°C	4	1	162	0	100 (?)
Rudenko 1993	A1+A2	2	7-14	<38.5°C	4	2	323	2	278
Rudenko 1996 I Yr 1	A1+A2	1	7-14	37.6°C-38.5°C	7	1	166	0	168
Rudenko 1996 I Yr 2	A1+A2	2	7-14	37.6°C-38.5°C	7	0	70	0	85
Rudenko 1996 I Yr 3	A1+A2	3	7-14	37.6°C-38.5°C	7	0	48	1	49
Rudenko 1991	A1	2	7-14	> 37.5°C	5	1	70	1	76
Rudenko 1991	B	2	7-14	> 37.5°C	5	0	89	1	76
Rudenko 1991	A1+B	2	7-14	> 37.5°C	5	0	86	1	76
Alexandrova 1986	A1+A2	2	7-15	37.6-38.5°C	5	1	100	0	90
Rudenko 1988	A1	2	7-15	>37.3°C	7 wd	0	286	0	168
Slepushkin 1988	A1	2	8-11	>= 37.5°C	5	1	43	1	38
Obrosova-Serova 1990	B	1	8-15	> 37.5°C ax	4	1	75	0	57
Obrosova-Serova 1990	B	2	8-15	> 37.5°C ax	4	0	58	0	45
Slepushkin 1991	A2	1	8-15	>= 37.6°C	? 4/5	0	97	0*	88*

Table 5. Live vaccine safety, RCTs, moderate temperature reactions (*Continued*)

Slepushkin 1991	A2	2	8-15	>= 37.6°C	? 4/5	2	95	0*	78*
Khan 1996	A1+A2+B	1	9-12	37.5°C-39.5°C	4	1	200	0	100 (?)
Over 38°C									
Steinhoff 1990 i	A2	1	6-48 m	>= 38.1°C	7	1	3	9	35
Steinhoff 1990 ii	A2	1	6-48 m	>= 38.1°C	7	2	5	9	35
Steinhoff 1990 iii	A2	1	6-48 m	>= 38.1°C	7	1	6	9	35
Steinhoff 1990 iv	A2	1	6-48 m	>= 38.1°C	7	3	7	9	35
Steinhoff 1990 v	A2	1	6-48 m	>= 38.1°C	7	1	12	9	35
Steinhoff 1991 i	A1	1	6-48 m	>= 38.1°C	7	0	6	10	43
Steinhoff 1991 ii	A1	1	6-48 m	>= 38.1°C	7	0	5	10	43
Steinhoff 1991 iii	A1	1	6-48 m	>= 38.1°C	7	5	17	10	43
Steinhoff 1991 iv	A1	1	6-48 m	>= 38.1°C	7	4	10	10	43
King 1990 i	A1+A2+B	1	18-71 m	> 38°C	10	2	59	4	122
King 1990 ii	A1+A2+B	1	18-71 m	> 38°C	10	4	56	4	122
King 1990 iii	A1+A2+B	1	18-71 m	> 38°C	10	7	56	4	122
King 1990 iv	A1+A2+B	1	18-71 m	> 38°C	10	0	63	4	122

Table 5. Live vaccine safety, RCTs, moderate temperature reactions (*Continued*)

Table 6. Live vaccine safety, RCTs, temperature reactions 38 °C and above

Study reference	Influenza types	Number of doses	Age group (years)	Temperature	Follow up (days)	n treatment	N treatment	n control	N control
Gruber 1997	A1+A2	1	2-6 m	>= 38.6°C rec, 38.1°C oral, 37.5°C ax	7	1	53	0	19
Gruber 1997	A1+A2	1	2-6 m	>= 38.6°C rec, 38.1°C oral, 37.5°C ax	7	4	60	0	19
Gruber 1997	A1+A2	1	2-6 m	>= 38.6°C rec, 38.1°C oral, 37.5°C ax	7	1	49	0	19
Steinhoff 1991 i	A1	1	6-48 m	>= 39.4°C	7	0	6	4	43
Steinhoff 1991 ii	A1	1	6-48 m	>= 39.4°C	7	0	5	4	43
Steinhoff 1991 iii	A1	1	6-48 m	>= 39.4°C	7	2	17	4	43
Steinhoff 1991 iv	A1	1	6-48 m	>= 39.4°C	7	0	10	4	43
Gruber 1997	A1+A2	1	7-18 m	>= 38.6°C rec, 38.1°C oral, 37.5°C ax	7	21	136	4	44
Gruber 1997	A1+A2	1	7-18 m	>= 38.6°C rec, 38.1°C oral, 37.5°C ax	7	16	131	4	44

Table 6. Live vaccine safety, RCTs, temperature reactions 38 °C and above (*Continued*)

Gruber 1997	A1+A2	1	7-18 m	>= 38.6°C rec, 38.1°C oral, 37.5°C ax	7	17	145	4	44
Gruber 1997	A1+A2	1	19-36 m	>= 38.6°C rec, 38.1°C oral, 37.5°C ax	7	18	189	5	61
Gruber 1997	A1+A2	1	19-36 m	>= 38.6°C rec, 38.1°C oral, 37.5°C ax	7	21	176	5	61
Gruber 1997	A1+A2	1	19-36 m	>= 38.6°C rec, 38.1°C oral, 37.5°C ax	7	24	186	5	61
Alexandrova 1986	A1+A2	2	3-6	>= 38.6°C	5	0	184	0	83
Rudenko 1996 I Yr 1	A1+A2	1	3-6	> 38.6°C	7	0	130	0	132
Rudenko 1996 I Yr 2	A1+A2	2	3-6	> 38.6°C	7	0	39	0	50
Rudenko 1996 I Yr 3	A1+A2	3	3-6	> 38.6°C	7	0	68	2	61
Desheva 2002	A1+A2+B	1 or 2	3-6	>= 38.6°C	5	0	184	0	72
Rudenko 1988	A1	2	3-6	Severe temp reaction	7 wd	0	164	0	132
Grigoreva 1994	A1	2	5-14	>= 38.6°C	4	0	128	0	98
Grigoreva 1994	A2	2	5-14	>= 38.6°C	4	0	125	0	98

Table 6. Live vaccine safety, RCTs, temperature reactions 38 °C and above (*Continued*)

Grigoreva 1994	B	2	5-14	>= 38.6°C	4	0	128	0	98
Grigoreva 1994	A1+A2+B	2	5-14	>= 38.6°C	4	0	135	0	98
Rudenko 1993	A1+A2	2	7-14	>= 38.5°C	4	0	162	0	100 (?)
Rudenko 1993	A1+A2	2	7-14	>= 38.5°C	4	0	323	0	278
Rudenko 1996 I Yr 1	A1+A2	1	7-14	> 38.6°C	7	0	166	0	168
Rudenko 1996 I Yr 2	A1+A2	2	7-14	> 38.6°C	7	0	70	0	85
Rudenko 1996 I Yr 3	A1+A2	3	7-14	> 38.6°C	7	0	48	0	49
Alexandrova 1986	A1+A2	2	7-15	>= 38.6°C	5	0	100	0	90
Rudenko 1988	A1	2	7-15	Severe temp reaction	7 wd	0	286	0	168

Table 7. Live vaccine safety, RCTs, other short-term outcomes, part 1

Study reference	Influenza type	Dose	Age group (years)	Outcome	Follow up (days)	n treatment	N treatment	n placebo	N placebo
Rhinorrhea/ Congestion									
Gruber 1997 i	A1+A2	1	2-18 months	Rhinnorrhea	7	93	189	31	62
Gruber 1997 ii	A1+A2	1	2-18 months	Rhinnorrhea	7	98	191	31	62

Table 7. Live vaccine safety, RCTs, other short-term outcomes, part 1 (*Continued*)

Gruber 1997 iii	A1+A2	1	2-18 months	Rhinnorrhea	7	109	191	31	62
Swierkosz 1994	A1+A2+B	3	2-22 months	Rhinorrhea 2 cons. days	11	7	13	1	1
Gruber 1996	A1	1	6-18 months	Increase in rhinorrhea	10	32	44	30	44
Gruber 1996	A2	1	6-18 months	Increase in rhinorrhea	10	32	45	30	44
Gruber 1996	A1+A2	1	6-18 months	Increase in rhinorrhea	10	35	47	30	44
Steinhoff 1990 i	A2	1	6-48 months	Rhinorrhea, pharyngitis or both	7	0	3	8	35
Steinhoff 1990 ii	A2	1	6-48 months	Rhinorrhea, pharyngitis or both	7	1	5	8	35
Steinhoff 1990 iii	A2	1	6-48 months	Rhinorrhea, pharyngitis or both	7	4	6	8	35
Steinhoff 1990 iv	A2	1	6-48 months	Rhinorrhea, pharyngitis or both	7	0	7	8	35
Steinhoff 1990 v	A2	1	6-48 months	Rhinorrhea, pharyngitis or both	7	0	12	8	35
Steinhoff 1991 i	A1	1	6-48 months	Rhinorrhea, pharyngitis or both	7	1	6	5	43
Steinhoff 1991 ii	A1	1	6-48 months	Rhinorrhea, pharyngitis or both	7	0	5	5	43

Table 7. Live vaccine safety, RCTs, other short-term outcomes, part 1 (*Continued*)

Steinhoff 1991 iii	A1	1	6-48 months	Rhinorrhea, pharyngitis or both	7	4	17	5	43
Steinhoff 1991 iv	A1	1	6-48 months	Rhinorrhea, pharyngitis or both	7	1	10	5	43
Zangwill 2001 a	A1+A2+B	1	1-3	Congestion/runny nose	10	64	100	49	100
Zangwill 2001 a	A1+A2+B	2	1-3	Congestion/runny nose	10	33	94	29	95
Zangwill 2001 b	A1+A2+B	1	1-3	Congestion/runny nose	10	68	100	49	100
Zangwill 2001 b	A1+A2+B	2	1-3	Congestion/runny nose	10	37	96	29	95
Zangwill 2001 c	A1+A2+B	1	1-3	Congestion/runny nose	10	65	100	49	100
Zangwill 2001 c	A1+A2+B	2	1-3	Congestion/runny nose	10	36	95	29	95
Zangwill 2001 d	A1+A2+B	1	1-3	Congestion/runny nose	10	63	100	49	100
Zangwill 2001 d	A1+A2+B	2	1-3	Congestion/runny nose	10	25	94	29	95
Belshe 1998	A1+A2+B	1&2	15-71 months	Rhinorrhea or nasal congestion	10	621	1070	250	532
Piedra 2002	A1+A2+B	1	15-71 months	Runny nose or nasal congestion	10	621	1070	256	532

Table 7. Live vaccine safety, RCTs, other short-term outcomes, part 1 (*Continued*)

Piedra 2002	A1+A2+B	2	15-71 months	Runny nose or nasal congestion	10	438	854	191	418
Piedra 2002	A1+A2+B	1	15-71 months	Runny nose or nasal congestion	2	276	1070	87	532
Piedra 2002	A1+A2+B	1	15-71 months	Runny nose or nasal congestion	3	307	1070	96	532
Piedra 2002	A1+A2+B	1	15-71 months	Runny nose or nasal congestion	8	307	1070	106	532
Piedra 2002	A1+A2+B	1	15-71 months	Runny nose or nasal congestion	9	291	1070	103	532
Piedra 2002	A1+A2+B	2	15-71 months	Runny nose or nasal congestion	2	187	854	80	418
Piedra 2002	A1+A2+B	2	15-71 months	Runny nose or nasal congestion	3	188	854	76	418
Piedra 2002	A1+A2+B	2	15-71 months	Runny nose or nasal congestion	8	198	854	79	418
Piedra 2002	A1+A2+B	2	15-71 months	Runny nose or nasal congestion	9	192	854	88	418
King 1990 i	A1+A2+B	1	18-71 months	Rhinorrhea	10	21	59	48	122
King 1990 ii	A1+A2+B	1	18-71 months	Rhinorrhea	10	25	56	48	122
King 1990 iii	A1+A2+B	1	18-71 months	Rhinorrhea	10	25	56	48	122
King 1990 iv	A1+A2+B	1	18-71 months	Rhinorrhea	10	20	63	48	122

Table 7. Live vaccine safety, RCTs, other short-term outcomes, part 1 (*Continued*)

Gruber 1997 i	A1+A2	1	19-36 months	Rhinnorrhea	7	82	155	21	47
Gruber 1997 ii	A1+A2	1	19-36 months	Rhinnorrhea	7	65	144	21	47
Gruber 1997 iii	A1+A2	1	19-36 months	Rhinnorrhea	7	68	144	21	47
Belshe 2000	A1+A2+B	1	26-85 months	Runny nose or nasal congestion	10	174	917	62	441
Piedra 2002	A1+A2+B	1	26-85 months	Runny nose or nasal congestion	10	387	917	187	441
Piedra 2002	A1+A+B	1	26-85 months	Runny nose or nasal congestion	2	170	917	58	441
Piedra 2002	A1+A2+B	1	26-85 months	Runny nose or nasal congestion	3	167	917	63	441
Piedra 2002	A1+A2+B	1	26-85 months	Runny nose or nasal congestion	8	138	917	65	441
Piedra 2002	A1+A2+B	1	26-85 months	Runny nose or nasal congestion	9	132	917	70	441
Rudenko 1991	A1	2	3-6	Rhinorrhea	5	0	53	0	54
Rudenko 1991	B	2	3-6	Rhinorrhea	5	0	44	0	54
Rudenko 1991	A1+B	2	3-6	Rhinorrhea	5	0	48	0	54
Rudenko 1991	A1	2	3-6	Nasal stuffiness	5	2	53	2	54
Rudenko 1991	B	2	3-6	Nasal stuffiness	5	2	44	2	54

Table 7. Live vaccine safety, RCTs, other short-term outcomes, part 1 (*Continued*)

Rudenko 1991	A1+B	2	3-6	Nasal stuffiness	5	0	48	2	54
Desheva 2002	A1+A2+B	1	3-6	Catarrh	5	1	184	0	72
Gruber 1990	A1+A2	1	3-18	Rhinorrhea or nasal congestion	14	9	58	15*	77*
Rudenko 1991	A1	2	7-14	Rhinorrhea	5	0	70	0	76
Rudenko 1991	B	2	7-14	Rhinorrhea	5	0	89	0	76
Rudenko 1991	A1+B	2	7-14	Rhinorrhea	5	0	86	0	76
Rudenko 1991	A1	2	7-14	Nasal stuffiness	5	3	70	1	76
Rudenko 1991	B	2	7-14	Nasal stuffiness	5	2	89	1	76
Rudenko 1991	A1+B	2	7-14	Nasal stuffiness	5	2	86	1	76
Slepushkin 1988	A1	2	8-11	Coryza	5	0	43	0	38
Nasal bleeding									
Rudenko 1991	A1	2	3-6	Nasal bleeding	5	0	53	0	54
Rudenko 1991	B	2	3-6	Nasal bleeding	5	0	44	0	54
Rudenko 1991	A1+B	2	3-6	Nasal bleeding	5	0	48	0	54

Table 7. Live vaccine safety, RCTs, other short-term outcomes, part 1 (*Continued*)

Rudenko 1991	A1	2	7-14	Nasal bleeding	5	0	70	0	76
Rudenko 1991	B	2	7-14	Nasal bleeding	5	0	89	0	76
Rudenko 1991	A1+B	2	7-14	Nasal bleeding	5	0	86	0	76
Sore throat									
Piedra 2002	A1+A2+B	1	15-71 months	Sore throat	10	104	1070	42	532
Piedra 2002	A1+A2+B	2	15-71 months	Sore throat	10	48	854	28	418
Piedra 2002	A1+A2+B	1	26-85 months	Sore throat	10	92	917	37	441
Zangwill 2001 a	A1+A2+B	1	1-3	Sore throat	10	8	100	9	100
Zangwill 2001 a	A1+A2+B	2	1-3	Sore throat	10	5	94	6	95
Zangwill 2001 b	A1+A2+B	1	1-3	Sore throat	10	7	100	9	100
Zangwill 2001 b	A1+A2+B	2	1-3	Sore throat	10	4	96	6	95
Zangwill 2001 c	A1+A2+B	1	1-3	Sore throat	10	4	100	9	100
Zangwill 2001 c	A1+A2+B	2	1-3	Sore throat	10	7	95	6	95
Zangwill 2001 d	A1+A2+B	1	1-3	Sore throat	10	4	100	9	100
Zangwill 2001 d	A1+A2+B	2	1-3	Sore throat	10	5	94	6	95
Slepushkin 1988	A1	2	8-11	Sore throat	5	1	43	1	38

Table 7. Live vaccine safety, RCTs, other short-term outcomes, part 1 (*Continued*)

King 1990 i	A1+A2+B	1	18-71 months	Sore throat	10	3	59	12	122
King 1990 ii	A1+A2+B	1	18-71 months	Sore throat	10	10	56	12	122
King 1990 iii	A1+A2+B	1	18-71 months	Sore throat	10	6	56	12	122
King 1990 iv	A1+A2+B	1	18-71 months	Sore throat	10	4	63	12	122
Rudenko 1991	A1	2	3-6	Sore throat	5	2	53	0	54
Rudenko 1991	A1	2	7-14	Sore throat	5	0	70	0	76
Rudenko 1991	B	2	3-6	Sore throat	5	1	44	0	54
Rudenko 1991	B	2	7-14	Sore throat	5	0	89	0	76
Rudenko 1991	A1+B	2	3-6	Sore throat	5	0	48	0	54
Rudenko 1991	A1+B	2	7-14	Sore throat	5	0	86	0	76
Slepushkin 1991	A2	1	8-15	Sore throat	4	0	97	0*	88*
Slepushkin 1991	A2	2	8-15	Sore throat	4	3	95	1*	78*

Table 8. Live vaccine safety, RCTs, other short-term outcomes, part 2

Study reference	Influenza type	Dose	Age group (years)	Outcome	Follow up (days)	n treatment	N treatment	n placebo	N placebo
Alexandrova 1986	A1+A2	2	3-6	Tonsillitis	5	2	2635	1	2988
Alexandrova 1986	A1+A2	2	7-15	Tonsillitis	5	3	13092	0	11240

Table 8. Live vaccine safety, RCTs, other short-term outcomes, part 2 (*Continued*)

Gruber 1996	A1	1	6-18 months	Cough	10	23	44	24	44
Gruber 1996	A2	1	6-18 months	Cough	10	23	45	24	44
Gruber 1996	A1+A2	1	6-18 months	Cough	10	19	47	24	44
Piedra 2002	A1+A2+B	1	15-71 months	Cough	10	296	1070	154	532
Piedra 2002	A1+A2+B	2	15-71 months	Cough	10	305	854	138	418
Piedra 2002	A1+A2+B	1	26-85 months	Cough	10	220	917	112	441
Zangwill 2001 a	A1+A2+B	1	1-3	Cough	10	23	100	24	100
Zangwill 2001 a	A1+A2+B	2	1-3	Cough	10	17	94	14	95
Zangwill 2001 b	A1+A2+B	1	1-3	Cough	10	33	100	24	100
Zangwill 2001 b	A1+A2+B	2	1-3	Cough	10	21	96	14	95
Zangwill 2001 c	A1+A2+B	1	1-3	Cough	10	21	100	24	100
Zangwill 2001 c	A1+A2+B	2	1-3	Cough	10	24	95	14	95
Zangwill 2001 d	A1+A2+B	1	1-3	Cough	10	15	100	24	100
Zangwill 2001 d	A1+A2+B	2	1-3	Cough	10	15	94	14	95
Gruber 1997 i	A1+A2	1	2-18 months	Cough	7	58	189	16	62
Gruber 1997 ii	A1+A2	1	2-18 months	Cough	7	57	161	16	62
Gruber 1997 iii	A1+A2	1	2-18 months	Cough	7	58	191	16	62

Table 8. Live vaccine safety, RCTs, other short-term outcomes, part 2 (*Continued*)

Gruber 1997 i	A1+A2	1	19-36 months	Cough	7	45	155	12	47
Gruber 1997 ii	A1+A2	1	19-36 months	Cough	7	33	144	12	47
Gruber 1997 iii	A1+A2	1	19-36 months	Cough	7	42	144	12	47
Slepushkin 1988	A1	2	8-11	Cough	5	0	43	0	38
King 1990 i	A1+A2+B	1	18-71 months	Cough	10	18	59	32	122
King 1990 ii	A1+A2+B	1	18-71 months	Cough	10	18	56	32	122
King 1990 iii	A1+A2+B	1	18-71 months	Cough	10	19	56	32	122
King 1990 iv	A1+A2+B	1	18-71 months	Cough	10	15	63	32	122
Rudenko 1991	A1	2	3-6	Cough	5	2	53	2	54
Rudenko 1991	A1	2	7-14	Cough	5	20	70	1	76
Rudenko 1991	B	2	3-6	Cough	5	2	44	2	54
Rudenko 1991	B	2	7-14	Cough	5	2	89	1	76
Rudenko 1991	A1+B	2	3-6	Cough	5	1	48	2	54
Rudenko 1991	A1+B	2	7-14	Cough	5	1	86	1	76
Slepushkin 1991	A2	1	8-15	Cough	? 4/5	0	97	1*	88*
Slepushkin 1991	A2	2	8-15	Cough	? 4/5	1	95	0*	78*

Table 8. Live vaccine safety, RCTs, other short-term outcomes, part 2 (*Continued*)

Swierkosz 1994	A1+A2+B	3	2-22 months	Cough >=2 episodes >=2 cons. days	11	2	13	1	1
Slepushkin 1991	A2	1	8-15	Head cold	? 4/5	0	97	0*	88*
Slepushkin 1991	A2	2	8-15	Head cold	? 4/5	0	95	4*	78*
Piedra 2002	A1+A2+B	1	15-71 months	Headache	10	84	1070	34	532
Piedra 2002	A1+A2+B	2	15-71 months	Headache	10	41	854	23	418
Piedra 2002	A1+A2+B	1	26-85 months	Headache	10	84	917	32	441
Zangwill 2001 a	A1+A2+B	1	1-3	Headache	10	6	100	2	100
Zangwill 2001 a	A1+A2+B	2	1-3	Headache	10	5	94	4	95
Zangwill 2001 b	A1+A2+B	1	1-3	Headache	10	10	100	2	100
Zangwill 2001 b	A1+A2+B	2	1-3	Headache	10	5	96	4	95
Zangwill 2001 c	A1+A2+B	1	1-3	Headache	10	11	100	2	100
Zangwill 2001 c	A1+A2+B	2	1-3	Headache	10	5	95	4	95
Zangwill 2001 d	A1+A2+B	1	1-3	Headache	10	8	100	2	100
Zangwill 2001 d	A1+A2+B	2	1-3	Headache	10	6	94	4	95
Slepushkin 1988	A1	2	8-11	Headache	5	1	43	1	38
Rudenko 1991	A1	2	3-6	Headache	5	0	53	1	54

Table 8. Live vaccine safety, RCTs, other short-term outcomes, part 2 (*Continued*)

Rudenko 1991	A1	2	7-14	Headache	5	2	70	3	76
Rudenko 1991	B	2	3-6	Headache	5	1	44	1	54
Rudenko 1991	B	2	7-14	Headache	5	1	89	3	76
Rudenko 1991	A1+B	2	3-6	Headache	5	2	48	1	54
Rudenko 1991	A1+B	2	7-14	Headache	5	3	86	3	76
Slepushkin 1991	A2	1	8-15	Headache	? 4/5	0	97	1*	88*
Slepushkin 1991	A2	2	8-15	Headache	? 4/5	5	95	3*	78*
Desheva 2002	A1+A2+B	1	3-6	Headache	5	1	184	0	72
Rudenko 1991	A1	2	3-6	Conjunctivitis	5	0	53	1	54
Rudenko 1991	A1	2	7-14	Conjunctivitis	5	0	70	0	76
Rudenko 1991	B	2	3-6	Conjunctivitis	5	0	44	1	54
Rudenko 1991	B	2	7-14	Conjunctivitis	5	0	89	0	76
Rudenko 1991	A1+B	2	3-6	Conjunctivitis	5	0	48	1	54
Rudenko 1991	A1+B	2	7-14	Conjunctivitis	5	0	86	0	76
Gruber 1996	A1	1	6-18 months	Otitis media	10	2	44	1	44
Gruber 1996	A2	1	6-18 months	Otitis media	10	2	45	1	44
Gruber 1996	A1+A2	1	6-18 months	Otitis media	10	2	47	1	44

Table 8. Live vaccine safety, RCTs, other short-term outcomes, part 2 (*Continued*)

Steinhoff 1990 i	A2	1	6-48 months	Otitis media	7	0	3	2	35
Steinhoff 1990 ii	A2	1	6-48 months	Otitis media	7	2	5	2	35
Steinhoff 1990 iii	A2	1	6-48 months	Otitis media	7	2	6	2	35
Steinhoff 1990 iv	A2	1	6-48 months	Otitis media	7	0	7	2	35
Steinhoff 1990 v	A2	1	6-48 months	Otitis media	7	0	12	2	35
Steinhoff 1991 i	A1	1	6-48 months	Otitis media	7	0	6	4	43
Steinhoff 1991 ii	A1	1	6-48 months	Otitis media	7	0	5	4	43
Steinhoff 1991 iii	A1	1	6-48 months	Otitis media	7	2	17	4	43
Steinhoff 1991 iv	A1	1	6-48 months	Otitis media	7	1	10	4	43
Belshe 1992	A1+A2+B	1	6 m-13 yrs	Otitis media	11	6	32	1	17
Swierkosz 1994	A1+A2+B	3	2-22 months	Otitis media	11	1	13	0	1

Table 9. Live vaccine safety, RCTs, other short-term outcomes, part 3

Study reference	Influenza types	Dose	Age groups (years)	Outcome	Follow up (days)	n treatment	N treatment	n placebo	N placebo
Piedra 2002	A1+A2+B	1	15-71 months	Chills	10	42	1070	18	532
Piedra 2002	A1+A2+B	2	15-71 months	Chills	10	27	854	12	418
Piedra 2002	A1+A2+B	1	26-85 months	Chills	10	31	917	13	441

Table 9. Live vaccine safety, RCTs, other short-term outcomes, part 3 (*Continued*)

Zangwill 2001 a	A1+A2+B	1	1-3	Chills	10	6	100	8	100
Zangwill 2001 a	A1+A2+B	2	1-3	Chills	10	7	94	0	95
Zangwill 2001 b	A1+A2+B	1	1-3	Chills	10	9	100	8	100
Zangwill 2001 b	A1+A2+B	2	1-3	Chills	10	6	96	0	95
Zangwill 2001 c	A1+A2+B	1	1-3	Chills	10	2	100	8	100
Zangwill 2001 c	A1+A2+B	2	1-3	Chills	10	4	95	0	95
Zangwill 2001 d	A1+A2+B	1	1-3	Chills	10	8	100	8	100
Zangwill 2001 d	A1+A2+B	2	1-3	Chills	10	3	94	0	95
Zangwill 2001 a	A1+A2+B	1	1-3	Muscle ache	10	8	100	6	100
Zangwill 2001 a	A1+A2+B	2	1-3	Muscle ache	10	3	94	3	95
Zangwill 2001 b	A1+A2+B	1	1-3	Muscle ache	10	7	100	6	100
Zangwill 2001 b	A1+A2+B	2	1-3	Muscle ache	10	4	96	3	95
Zangwill 2001 c	A1+A2+B	1	1-3	Muscle ache	10	3	100	6	100
Zangwill 2001 c	A1+A2+B	2	1-3	Muscle ache	10	3	95	3	95
Zangwill 2001 d	A1+A2+B	1	1-3	Muscle ache	10	6	100	6	100
Zangwill 2001 d	A1+A2+B	2	1-3	Muscle ache	10	2	94	3	95
Piedra 2002	A1+A2+B	1	15-71 months	Muscle aches	10	55	1070	14	532

Table 9. Live vaccine safety, RCTs, other short-term outcomes, part 3 (*Continued*)

Piedra 2002	A1+A2+B	2	15-71 months	Muscle aches	10	23	854	7	418
Piedra 2002	A1+A2+B	1	26-85 months	Muscle aches	10	26	917	16	441
Piedra 2002	A1+A2+B	1	15-71 months	Muscle aches	0	3	1070	2	532
Piedra 2002	A1+A2+B	1	15-71 months	Muscle aches	1	3	1070	0	532
Piedra 2002	A1+A2+B	1	15-71 months	Muscle aches	2	14	1070	2	532
Piedra 2002	A1+A2+B	1	15-71 months	Muscle aches	3	4	1070	2	532
Piedra 2002	A1+A2+B	1	15-71 months	Muscle aches	4	6	1070	2	532
Piedra 2002	A1+A2+B	1	15-71 months	Muscle aches	5	8	1070	2	532
Piedra 2002	A1+A2+B	1	15-71 months	Muscle aches	6	3	1070	0	532
Piedra 2002	A1+A2+B	1	15-71 months	Muscle aches	7	2	1070	1	532
Piedra 2002	A1+A2+B	1	15-71 months	Muscle aches	8	3	1070	0	532
Piedra 2002	A1+A2+B	1	15-71 months	Muscle aches	9	4	1070	2	532
Piedra 2002	A1+A2+B	1	15-71 months	Muscle aches	10	5	1070	1	532
Piedra 2002	A1+A2+B	1	15-71 months	Irritability	10	276	1070	137	532
Piedra 2002	A1+A2+B	2	15-71 months	Irritability	10	142	854	77	418
Piedra 2002	A1+A2+B	1	26-85 months	Irritability	10	132	917	71	441
Piedra 2002	A1+A2+B	1	15-71 months	Irritability	2	89	1070	25	532

Table 9. Live vaccine safety, RCTs, other short-term outcomes, part 3 (*Continued*)

Piedra 2002	A1+A2+B	1	15-71 months	Irritability	3	76	1070	29	532
Piedra 2002	A1+A2+B	1	15-71 months	Irritability	8	47	1070	15	532
Piedra 2002	A1+A2+B	1	15-71 months	Irritability	9	41	1070	18	532
Piedra 2002	A1+A2+B	2	15-71 months	Irritability	2	38	854	14	418
Piedra 2002	A1+A2+B	2	15-71 months	Irritability	3	26	854	14	418
Piedra 2002	A1+A2+B	2	15-71 months	Irritability	8	19	854	20	418
Piedra 2002	A1+A2+B	2	15-71 months	Irritability	9	18	854	20	418
Piedra 2002	A1+A2+B	1	26-85 months	Irritability	2	34	917	17	441
Piedra 2002	A1+A2+B	1	26-85 months	Irritability	3	28	917	10	441
Piedra 2002	A1+A2+B	1	26-85 months	Irritability	8	22	917	22	441
Piedra 2002	A1+A2+B	1	26-85 months	Irritability	9	17	917	17	441
Zangwill 2001 a	A1+A2+B	1	1-3	Irritability	10	37	100	33	100
Zangwill 2001 a	A1+A2+B	2	1-3	Irritability	10	23	94	24	95
Zangwill 2001 b	A1+A2+B	1	1-3	Irritability	10	35	100	33	100
Zangwill 2001 b	A1+A2+B	2	1-3	Irritability	10	25	96	24	95
Zangwill 2001 c	A1+A2+B	1	1-3	Irritability	10	32	100	33	100
Zangwill 2001 c	A1+A2+B	2	1-3	Irritability	10	23	95	24	95

Table 9. Live vaccine safety, RCTs, other short-term outcomes, part 3 (*Continued*)

Zangwill 2001 d	A1+A2+B	1	1-3	Irritability	10	35	100	33	100
Zangwill 2001 d	A1+A2+B	2	1-3	Irritability	10	20	94	24	95
King 1990 i	A1+A2+B	1	18-71 months	Irritability	10	14	59	27	122
King 1990 ii	A1+A2+B	1	18-71 months	Irritability	10	20	56	27	122
King 1990 iii	A1+A2+B	1	18-71 months	Irritability	10	13	56	27	122
King 1990 iv	A1+A2+B	1	18-71 months	Irritability	10	17	63	27	122
Belshe 1998	A1+A2+B	1&2	15-71 months	Decreased activity	10	171	1070	64	532
Piedra 2002	A1+A2+B	1	15-71 months	Decreased activity	10	170	1070	68	532
Piedra 2002	A1+A2+B	2	15-71 months	Decreased activity	10	109	854	52	418
Piedra 2002	A1+A2+B	1	26-85 months	Decreased activity	10	104	917	56	441
Piedra 2002	A1+A2+B	1	15-71 months	Decreased activity	2	61	1070	11	532
Piedra 2002	A1+A2+B	1	15-71 months	Decreased activity	3	47	1070	14	532
Piedra 2002	A1+A2+B	1	15-71 months	Decreased activity	8	29	1070	5	532
Piedra 2002	A1+A2+B	1	15-71 months	Decreased activity	9	24	1070	5	532
Piedra 2002	A1+A2+B	2	15-71 months	Decreased activity	2	24	854	6	418
Piedra 2002	A1+A2+B	2	15-71 months	Decreased activity	3	18	854	8	418

Table 9. Live vaccine safety, RCTs, other short-term outcomes, part 3 (*Continued*)

Piedra 2002	A1+A2+B	2	15-71 months	Decreased activity	8	19	854	12	418
Piedra 2002	A1+A2+B	2	15-71 months	Decreased activity	9	14	854	17	418
Piedra 2002	A1+A2+B	1	26-85 months	Decreased activity	2	25	917	11	441
Piedra 2002	A1+A2+B	1	26-85 months	Decreased activity	3	19	917	10	441
Piedra 2002	A1+A2+B	1	26-85 months	Decreased activity	8	9	917	14	441
Piedra 2002	A1+A2+B	1	26-85 months	Decreased activity	9	15	917	12	441
Zangwill 2001 a	A1+A2+B	1	1-3	Decreased activity	10	13	100	16	100
Zangwill 2001 a	A1+A2+B	2	1-3	Decreased activity	10	15	94	10	95
Zangwill 2001 b	A1+A2+B	1	1-3	Decreased activity	10	20	100	46	100
Zangwill 2001 b	A1+A2+B	2	1-3	Decreased activity	10	21	96	10	95
Zangwill 2001 c	A1+A2+B	1	1-3	Decreased activity	10	14	100	16	100
Zangwill 2001 c	A1+A2+B	2	1-3	Decreased activity	10	11	95	10	95
Zangwill 2001 d	A1+A2+B	1	1-3	Decreased activity	10	21	100	16	100
Zangwill 2001 d	A1+A2+B	2	1-3	Decreased activity	10	8	94	10	95
Rudenko 1991	A1	2	3-6	Malaise	5	4	53	2	54
Rudenko 1991	A1	2	7-14	Malaise	5	4	70	2	76

Table 9. Live vaccine safety, RCTs, other short-term outcomes, part 3 (*Continued*)

Rudenko 1991	B	2	3-6	Malaise	5	3	44	2	54
Rudenko 1991	B	2	7-14	Malaise	5	1	89	2	76
Rudenko 1991	A1+B	2	3-6	Malaise	5	1	48	2	54
Rudenko 1991	A1+B	2	7-14	Malaise	5	1	86	2	76

Table 10. Key to safety tables

Symbol	Key
I, II, etc	Different papers, same author, same year
a, b, c	Same study, same vaccine, >1 groups
i,ii,iii	Same vaccine different doses
Yr1, Yr2 etc	Same children received vaccine >1 years
Whole?	Reference to whole/split/recombinant not made in text, therefore probably whole vaccine
A1	Influenza A(H1N1)
A2	Influenza A(H3N2)
wd	working days
*	n/N for placebo combined for intranasal and intramuscular placebos
(?)	N for placebo not clear from paper
ax	axillary
rec	rectal
(1)	infants and younger children
(2)	older children

Reactions to live vaccine within six weeks of inoculation were included in one RCTs and one cohort study. Belshe 1998 included serious adverse events up to 42 days after vaccination; none were reported. From the same trial, Piedra 2002a 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; otitis media. Vasil'eva 1988b included requests for urgent medical attention and hospitalisation from a cohort study.

For longer term outcomes, up to six months after inoculation Belshe 1998 included vaccine related 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 ARI) and other somatic illnesses. Rudenko 1988 included only morbidity (excluding influenza and ARI). Rudenko 1996a included 13 outcomes including allergies and five respiratory tract disease outcomes. All of the medium and long term outcome data for live vaccine safety in presented in additional Table 11.

Table 11. Live vaccine safety, RCTs, other short-term outcomes, part 4

Study reference	Influenza type	Dose	Age group (years)	Outcome	Follow up	n treatment	N treatment	n placebo	N placebo
Gruber 1997 i	A1+A2	1	2-18 months	Any respiratory symptom	7	102	189	38	62
Gruber 1997 ii	A1+A2	1	2-18 months	Any respiratory symptom	7	110	191	38	62
Gruber 1997 iii	A1+A2	1	2-18 months	Any respiratory symptom	7	117	191	38	62
Gruber 1997 i	A1+A2	1	19-36 months	Any respiratory symptom	7	91	155	24	47
Gruber 1997 ii	A1+A2	1	19-36 months	Any respiratory symptom	7	70	144	24	47
Gruber 1997 iii	A1+A2	1	19-36 months	Any respiratory symptom	7	78	144	24	47

Table 11. Live vaccine safety, RCTs, other short-term outcomes, part 4 (*Continued*)

Alexandrova 1986	A1+A2	2	3-6	Bronchitis	5	1	2635	1	2988
Alexandrova 1986	A1+A2	2	7-15	Bronchitis	5	1	13092	0	11240
Steinhoff 1990 i	A2	1	6-48 months	Illness attrib. influenza A	7	0	3	2	35
Steinhoff 1990 ii	A2	1	6-48 months	Illness attrib. influenza A	7	2	5	2	35
Steinhoff 1990 iii	A2	1	6-48 months	Illness attrib. influenza A	7	2	6	2	35
Steinhoff 1990 iv	A2	1	6-48 months	Illness attrib. influenza A	7	2	7	2	35
Steinhoff 1990 v	A2	1	6-48 months	Illness attrib. influenza A	7	1	12	2	35
Alexandrova 1986	A1+A2	2	3-6	Influenza and respiratory disease	5	15	2635	27	2988
Alexandrova 1986	A1+A2	2	7-15	Influenza and respiratory disease	5	23	13092	13	11240
Steinhoff 1990 i	A2	1	6-48 months	Influenza-like illness	7	1	3	13	35
Steinhoff 1990 ii	A2	1	6-48 months	Influenza-like illness	7	2	5	13	35
Steinhoff 1990 iii	A2	1	6-48 months	Influenza-like illness	7	5	6	13	35
Steinhoff 1990 iv	A2	1	6-48 months	Influenza-like illness	7	3	7	13	35

Table 11. Live vaccine safety, RCTs, other short-term outcomes, part 4 (*Continued*)

Steinhoff 1990 v	A2	1	6-48 months	Influenza-like illness	7	1	12	13	35
Steinhoff 1991 i	A1	1	6-48 months	Lower respiratort tract illness (wheezing or cough)	7	0	6	3	43
Steinhoff 1991 ii	A1	1	6-48 months	Lower respiratort tract illness (wheezing or cough)	7	0	5	3	43
Steinhoff 1991 iii	A1	1	6-48 months	Lower respiratort tract illness (wheezing or cough)	7	1	17	3	43
Steinhoff 1991 iv	A1	1	6-48 months	Lower respiratort tract illness (wheezing or cough)	7	0	10	3	43
Swierkosz 1994	A1+A2+B	3	2-22 months	Lower respiratory infection (wheezing or pneumonia)	11	0	13	0	1
Belshe 1992	A1+A2+B	1	6 months-13 yrs	Lower respirtaory illness	11	0	32	1	17
King 1990 i	A1+A2+B	1	18-71 months	Any illness	10	35	59	65	122
King 1990 ii	A1+A2+B	1	18-71 months	Any illness	10	33	56	65	122
King 1990 iii	A1+A2+B	1	18-71 months	Any illness	10	36	56	65	122
King 1990 iv	A1+A2+B	1	18-71 months	Any illness	10	31	63	65	122

Table 11. Live vaccine safety, RCTs, other short-term outcomes, part 4 (*Continued*)

Piedra 2002	A1+A2+B	1	15-71 months	Antibiotic use	10	50	1070	18	532
Piedra 2002	A1+A2+B	2	15-71 months	Antibiotic use	10	58	854	26	418
Piedra 2002	A1+A2+B	1	26-85 months	Antibiotic use	10	46	917	22	441
Piedra 2002	A1+A2+B	1	15-71 months	Antihistamine use	10	215	1070	101	532
Piedra 2002	A1+A2+B	2	15-71 months	Antihistamine use	10	174	854	88	418
Piedra 2002	A1+A2+B	1	26-85 months	Antihistamine use	10	164	917	71	441
Piedra 2002	A1+A2+B	1	15-71 months	Antipyretic use	10	251	1070	88	532
Piedra 2002	A1+A2+B	2	15-71 months	Antipyretic use	10	109	854	63	418
Piedra 2002	A1+A2+B	1	26-85 months	Antipyretic use	10	134	917	64	441
Grigoreva 2002	A1+A2+B	2	7-14	Children consulting doctor with ARI symptoms	7	15	675	19	369
Grigoreva 2002	A1+A2+B	2	7-14	Allergic reactions	7	1	675	0	369
Grigoreva 2002	A1+A2+B	1	7-14	Children consulting doctor with ARI symptoms	7	10	971	10	471
Grigoreva 2002	A1+A2+B	1	7-14	Allergic reactions	7	2	971	0	471

The following short-term outcomes were presented in the trials of inactivated vaccines:

Temperature - seven RCTs and three cohort studies.

Local reactions - seven RCTs and two cohort studies including erythema (three RCTs); hyperemia (one RCT, two cohorts); infiltration (one RCT, one cohort); local pain (two RCTs, one cohort); swelling (two RCTs), unspecified local reactions (two RCTs). The full list of outcomes is presented in additional Table 12.

Headache - four RCTs, one cohort study.

Gastro-intestinal symptoms - three RCTs.

Respiratory tract symptoms - two RCTs and two cohort studies.

General symptoms including malaise, muscle aches - five RCTs, one cohort study.

School absence - one RCT. Several other miscellaneous outcomes are reported in Table 13, Table 14 and Table 15.

Table 12. Inactivated vaccine safety, RCTs, one dose, local reactions

Study reference	Vaccine type	Influenza types	Age group (years)	Outcome	Follow up (days)	n treatment	N treatment	n placebo	N placebo
Erythema									
Wright 1976	Whole?	B	12-28 months	Erythema >= 10mm	2	1	16	0	19
Wright 1976	Whole?	B	3-6	Erythema >= 10mm	2	12	29	0	4
Beutner 1979	Whole?	A2	7-14	Erythema	7	90	300	19	275
Hyperemia									
Vasilyeva 1998 I	Whole Vaccine 1	A1+A2	11-14	Slight hyperemia <= 25mm	5	36	85	7	86
Vasilyeva 1998 I	Whole Vaccine 1	A1+A2	11-14	Moderate hyperemia 26-50mm	5	30	85	0	86
Vasilyeva 1998 I	Whole Vaccine 2	A1+A2	11-14	Slight hyperemia <= 25mm	5	52	87	7	86

Table 12. Inactivated vaccine safety, RCTs, one dose, local reactions (*Continued*)

Vasilyeva 1998 I	Whole Vaccine 2	A1+A2	11-14	Moderate hyperemia 26-50mm	5	0	87	0	86
Vasilyeva 1998 I	Whole Vaccine 3	A1+A2	11-14	Slight hyperemia <= 25mm	5	36	270	3	252
Vasilyeva 1998 I	Whole Vaccine 3	A1+A2	11-14	Moderate hyperemia 26-50mm	5	27	270	0	252
Infiltration									
Vasilyeva 1998 I	Whole Vaccine 1	A1+A2	11-14	Slight infiltration of skin <= 25mm	5	20	85	4	86
Vasilyeva 1998 I	Whole Vaccine 1	A1+A2	11-14	Moderate infiltration of skin 26-50mm	5	1	85	0	86
Vasilyeva 1998 I	Whole Vaccine 2	A1+A2	11-14	Slight infiltration of skin <= 25mm	5	24	87	4	86
Vasilyeva 1998 I	Whole Vaccine 2	A1+A2	11-14	Moderate infiltration of skin 26-50mm	5	1	87	0	86
Vasilyeva 1998 I	Whole Vaccine 3	A1+A2	11-14	Slight infiltration of skin <= 25mm	5	23	270	0	252
Vasilyeva 1998 I	Whole Vaccine 3	A1+A2	11-14	Moderate infiltration of skin 26-50mm	5	3	270	0	252
Swelling/ induration									

Table 12. Inactivated vaccine safety, RCTs, one dose, local reactions (*Continued*)

Wright 1976	Whole?	B	12-28 months	Swelling/ induration	2	1	16	0	19
Wright 1976	Whole?	B	3-6	Swelling/ induration	2	8	29	0	4
Beutner 1979	Whole?	A2	7-14	Local swelling	7	33	300	0	275
Pain/ tenderness									
Gruber 1990	Subvirion	A1+A2+B	3-18	Tenderness at injection site	14	11	54	7	77*
Beutner 1979	Whole?	A2	7-14	Local pain, tenderness	7	60	300	47	275
Unspecified local reactions									
Gutman 1977	Whole	A1	3-6	Local reactions	1	0	10	0	12
Gutman 1977	Split	A1	3-6	Local reactions	1	2	24	0	12
Gutman 1977	Whole	A1	6-10	Local reactions	1	4	24	0	6
Gutman 1977	Split	A1	6-10	Local reactions	1	8	40	0	6
Slepushkin 1991	Whole?	A2	8-15	Local reactions <= 25mm	? 4/5	30	56	1	44
Slepushkin 1991	Whole?	A2	8-15	Local reactions 26-50mm	? 4/5	1	56	0	44
Slepushkin 1991	Whole?	A2	8-15	Local reactions >= 50mm	? 4/5	0	56	0	44

Table 12. Inactivated vaccine safety, RCTs, one dose, local reactions (*Continued*)

Table 13. Inactivated vaccine safety, RCTs, one dose, outcomes up to 6 months

Study reference	Vaccine types	Influenza types	Age group (years)	Outcome	Follow - up	n treatment	N treatment	n control	N control
Vasilyeva 1988 I	Whole Vaccine 1	A1+A2	11-14	Illnesses of ear, nose and throat	6 months	10	4655	10	3493
Vasilyeva 1988 I	Whole Vaccine 2	A1+A2	11-14	Illnesses of ear, nose and throat	6 months	13	6625	10	3493
Vasilyeva 1988 I	Whole Vaccine 3	A1+A2	11-14	Illnesses of ear, nose and throat	6 months	0	491	10	3493
Vasilyeva 1988 I	Whole Vaccine 1	A1+A2	11-14	Tonsillitis & acute chronic tonsillitis	6 months	50	4655	42	3493
Vasilyeva 1988 I	Whole Vaccine 2	A1+A2	11-14	Tonsillitis & acute chronic tonsillitis	6 months	66	6625	42	3493
Vasilyeva 1988 I	Whole Vaccine 3	A1+A2	11-14	Tonsillitis & acute chronic tonsillitis	6 months	5	491	42	3493
Vasilyeva 1988 I	Whole Vaccine 1	A1+A2	11-14	Bronchitis	6 months	17	4655	17	3493
Vasilyeva 1988 I	Whole Vaccine 2	A1+A2	11-14	Bronchitis	6 months	27	6625	17	3493
Vasilyeva 1988 I	Whole Vaccine 3	A1+A2	11-14	Bronchitis	6 months	3	491	17	3493
Vasilyeva 1988 I	Whole Vaccine 1	A1+A2	11-14	Inflammation of lungs	6 months	2	4655	2	3493

Table 13. Inactivated vaccine safety, RCTs, one dose, outcomes up to 6 months (*Continued*)

Vasilyeva 1988 I	Whole Vaccine 2	A1+A2	11-14	Inflammation of lungs	6 months	0	6625	2	3493
Vasilyeva 1988 I	Whole Vaccine 3	A1+A2	11-14	Inflammation of lungs	6 months	0	491	2	3493
Vasilyeva 1988 I	Whole Vaccine 1	A1+A2	11-14	Allergies	6 months	2	4655	2	3493
Vasilyeva 1988 I	Whole Vaccine 2	A1+A2	11-14	Allergies	6 months	1	6625	2	3493
Vasilyeva 1988 I	Whole Vaccine 3	A1+A2	11-14	Allergies	6 months	0	491	2	3493
Vasilyeva 1988 I	Whole Vaccine 1	A1+A2	11-14	Acute chronic stomach illnesses	6 months	2	4655	3	3493
Vasilyeva 1988 I	Whole Vaccine 2	A1+A2	11-14	Acute chronic stomach illnesses	6 months	2	6625	3	3493
Vasilyeva 1988 I	Whole Vaccine 3	A1+A2	11-14	Acute chronic stomach illnesses	6 months	1	491	3	3493
Vasilyeva 1988 I	Whole Vaccine 1	A1+A2	11-14	Stomach or duodenal ulcer	6 months	1	4655	1	3493
Vasilyeva 1988 I	Whole Vaccine 2	A1+A2	11-14	Stomach or duodenal ulcer	6 months	0	6625	1	3493
Vasilyeva 1988 I	Whole Vaccine 3	A1+A2	11-14	Stomach or duodenal ulcer	6 months	0	491	1	3493
Vasilyeva 1988 I	Whole Vaccine 1	A1+A2	11-14	Acute intestinal illness	6 months	2	4655	2	3493

Table 13. Inactivated vaccine safety, RCTs, one dose, outcomes up to 6 months (*Continued*)

Vasilyeva 1988 I	Whole Vaccine 2	A1+A2	11-14	Acute intestinal illness	6 months	0	6625	2	3493
Vasilyeva 1988 I	Whole Vaccine 3	A1+A2	11-14	Acute intestinal illness	6 months	0	491	2	3493
Vasilyeva 1988 I	Whole Vaccine 1	A1+A2	11-14	Heart illness	6 months	0	4655	0	3493
Vasilyeva 1988 I	Whole Vaccine 2	A1+A2	11-14	Heart illness	6 months	0	6625	0	3493
Vasilyeva 1988 I	Whole Vaccine 3	A1+A2	11-14	Heart illness	6 months	0	491	0	3493
Vasilyeva 1988 I	Whole Vaccine 1	A1+A2	11-14	Kidney illnesses	6 months	1	4655	0	3493
Vasilyeva 1988 I	Whole Vaccine 2	A1+A2	11-14	Kidney illnesses	6 months	2	6625	0	3493
Vasilyeva 1988 I	Whole Vaccine 3	A1+A2	11-14	Kidney illnesses	6 months	0	491	0	3493
Vasilyeva 1988 I	Whole Vaccine 1	A1+A2	11-14	Carbuncles, furuncles, hidradenitis	6 months	2	4655	2	3493
Vasilyeva 1988 I	Whole Vaccine 2	A1+A2	11-14	Carbuncles, furuncles, hidradenitis	6 months	2	6625	2	3493
Vasilyeva 1988 I	Whole Vaccine 3	A1+A2	11-14	Carbuncles, furuncles, hidradenitis	6 months	0	491	2	3493
Vasilyeva 1988 I	Whole Vaccine 1	A1+A2	11-14	Other illnesses of the skin	6 months	4	4655	1	3493

Table 13. Inactivated vaccine safety, RCTs, one dose, outcomes up to 6 months (*Continued*)

Vasilyeva 1988 I	Whole Vaccine 2	A1+A2	11-14	Other illnesses of the skin	6 months	3	6625	1	3493
Vasilyeva 1988 I	Whole Vaccine 3	A1+A2	11-14	Other illnesses of the skin	6 months	0	491	1	3493
Vasilyeva 1988 I	Whole Vaccine 1	A1+A2	11-14	Neuralgia, neuritis, radiculagia	6 months	0	4655	0	3493
Vasilyeva 1988 I	Whole Vaccine 2	A1+A2	11-14	Neuralgia, neuritis, radiculagia	6 months	0	6625	0	3493
Vasilyeva 1988 I	Whole Vaccine 3	A1+A2	11-14	Neuralgia, neuritis, radiculagia	6 months	0	491	0	3493
Vasilyeva 1988 I	Whole Vaccine 1	A1+A2	11-14	Other illnesses of nervous system	6 months	1	4655	1	3493
Vasilyeva 1988 I	Whole Vaccine 2	A1+A2	11-14	Other illnesses of nervous system	6 months	1	6625	1	3493
Vasilyeva 1988 I	Whole Vaccine 3	A1+A2	11-14	Other illnesses of nervous system	6 months	0	491	1	3493
Vasilyeva 1988 I	Whole Vaccine 1	A1+A2	11-14	Other illnesses	6 months	42	4655	3	3493
Vasilyeva 1988 I	Whole Vaccine 2	A1+A2	11-14	Other illnesses	6 months	40	6625	3	3493
Vasilyeva 1988 I	Whole Vaccine 3	A1+A2	11-14	Other illnesses	6 months	4	491	3	3493

Table 14. Inactivated vaccine safety, cohort studies, 1 dose

Study reference	Vaccine type	Influenza types	Age group (years)	Outcome	Follow up (days)	n treatment	N treatment	n control	N control
Vasilyeva 1982	Whole? Injector	A2	7-10	Temperature 37-37.5°C	5	14	70	8	44
Vasilyeva 1982	Whole? Syringe	A2	7-10	Temperature 37-37.5°C	5	11	43	10	38
Vasilyeva 1988 II	Whole	A1+A2	11-14	Temperature 37-37.5°C	5	71	434	48	336
Vasilyeva 1982	Whole? Injector	A2	11-15	Temperature 37-37.5°C	5	3	35	4	37
Vasilyeva 1982	Whole? Syringe	A2	11-15	Temperature 37-37.5°C	5	4	34	4	33
Vasilyeva 1988 II	Whole	A1+A2	11-14	Temperature >= 37.6°C	5	1	434	2	336
Vasilyeva 1982	Whole? Injector	A2	7-10	Temperature 37.6-38.5°C	5	1	70	1	44
Vasilyeva 1982	Whole? Syringe	A2	7-10	Temperature 37.6-38.5°C	5	1	43	0	38
Vasilyeva 1982	Whole? Injector	A2	11-15	Temperature 37.6-38.5°C	5	1	35	1	37
Vasilyeva 1982	Whole? Syringe	A2	11-15	Temperature 37.6-38.5°C	5	0	34	1	33
Slepushkin 1994 b	Whole?	A1+A2	7-10	Temperature 37.6-38.5°C	Unspecified	5	271	2*	278*
Slepushkin 1994 a	Whole?	A1+A2	7-14	Temperature 37.6-38.5°C	Unspecified	0	76	0*	272*

Table 14. Inactivated vaccine safety, cohort studies, 1 dose (*Continued*)

Slepushkin 1994 b	Whole?	A1+A2	11-14	Temperature 37.6-38.5°C	Unspecified	8	435	2*	278*
Slepushkin 1994 b	Whole?	A1+A2	7-10	Temperature > 38.6°C	Unspecified	0	271	0*	272*
Slepushkin 1994 a	Whole?	A1+A2	7-14	Temperature > 38.6°C	Unspecified	0	76	0*	272*
Slepushkin 1994 b	Whole?	A1+A2	11-14	Temperature > 38.6°C	Unspecified	3	435	0*	278*
Vasilyeva 1982	Whole? Injector	A2	7-10	Sore throat	5	11	70	8	44
Vasilyeva 1982	Whole? Syringe	A2	7-10	Sore throat	5	13	43	8	38
Vasilyeva 1982	Whole? Injector	A2	11-15	Sore throat	5	4	35	5	37
Vasilyeva 1982	Whole? Syringe	A2	11-15	Sore throat	5	11	34	3	33
Vasilyeva 1988 II	Whole	A1+A2	11-14	Intoxication & catarrh in nasopharynx	5	22	434	8	336
Vasilyeva 1982	Whole? Injector	A2	7-10	Intoxication (headache or malaise)	5	1	70	1	44
Vasilyeva 1982	Whole? Syringe	A2	7-10	Intoxication (headache or malaise)	5	3	43	1	38
Vasilyeva 1982	Whole? Injector	A2	11-15	Intoxication (headache or malaise)	5	1	35	2	37

Table 14. Inactivated vaccine safety, cohort studies, 1 dose (*Continued*)

Vasilyeva 1982	Whole? Syringe	A2	11-15	Intoxication (headache or malaise)	5	4	34	1	33
Vasilyeva 1988 II	Whole	A1+A2	11-14	Hyperemia <= 25mm	5	314	434	40	336
Vasilyeva 1982	Whole? Injector	A2	7-10	Hyperemia/ cutaneous wheal 0.5-2.5 cm	5	28	70	1	44
Vasilyeva 1982	Whole? Syringe	A2	7-10	Hyperemia/ cutaneous wheal 0.5-2.5 cm	5	40	43	13	38
Vasilyeva 1982	Whole? Injector	A2	11-15	Hyperemia/ cutaneous wheal 0.5-2.5 cm	5	27	35	4	37
Vasilyeva 1982	Whole? Syringe	A2	11-15	Hyperemia/ cutaneous wheal 0.5-2.5 cm	5	25	34	2	33
Vasilyeva 1988 II	Whole	A1+A2	11-14	Hyperemia >= 26mm	5	35	434	1	336
Vasilyeva 1982	Whole? Injector	A2	7-10	Hyperemia/ cutaneous wheal 2.5-4.9 cm	5	0	70	0	44
Vasilyeva 1982	Whole? Syringe	A2	7-10	Hyperemia/ cutaneous wheal 2.5-4.9 cm	5	0	43	0	38

Table 14. Inactivated vaccine safety, cohort studies, 1 dose (*Continued*)

Vasilyeva 1982	Whole? Injector	A2	11-15	Hyperemia/ cutaneous wheal 2.5-4.9 cm	5	1	35	0	37
Vasilyeva 1982	Whole? Syringe	A2	11-15	Hyperemia/ cutaneous wheal 2.5-4.9 cm	5	9	34	0	33
Vasilyeva 1988 II	Whole	A1+A2	11-14	Infiltration <= 25mm	5	143	434	6	336
Vasilyeva 1988 II	Whole	A1+A2	11-14	Infiltration >= 26mm	5	4	434	0	336
Vasilyeva 1988 II	Whole	A1+A2	11-14	Pain at administration site	5	23	434	4	336
Elshina 2000	Polymer subunit	A1+A2+B	6-14	Headache	5	1	40	1	40
Elshina 2000	Polymer subunit	A1+A2+B	6-14	Cough	5 5	1	40	0	40
Elshina 2000	Polymer subunit	A1+A2+B	6-14	Sore throat	5	1	40	0	40
Elshina 2000	Polymer subunit	A1+A2+B	6-14	Head cold	5	1	40	1	40
Elshina 2000	Polymer subunit	A1+A2+B	14-17	Feeling unwell	5	5	30	3	30
Elshina 2000	Polymer subunit	A1+A2+B	14-17	Headache	5	4	30	6	30
Elshina 2000	Polymer subunit	A1+A2+B	14-17	Cough	5	1	30	2	30
Elshina 2000	Polymer subunit	A1+A2+B	14-17	Sore throat	5	3	30	2	30
Elshina 2000	Polymer subunit	A1+A2+B	14-17	Head cold	5	0	30	2	30

Table 14. Inactivated vaccine safety, cohort studies, 1 dose (*Continued*)

Vasilyeva 1988 II	Whole	A1+A2	11-14	Request urgent medical attention	30	25	5074	11	2135
Vasilyeva 1988 II	Whole	A1+A2	11-14	Hospitalisation	30	5	5074	0	2135
Vasilyeva 1988 II	Whole	A1+A2	11-14	Morbidity of all nosological forms (except influenza and ARI)	30	127	5074	30	2135
Elshina 2000	Polymer subunit	A1+A2+B	14-17	URTI (excluding influenza & ARI)	5 months	8	930	19	905
Elshina 2000	Polymer subunit	A1+A2+B	6-17	Infectious illnesses	5 months	12	930	10	905
Elshina 2000	Polymer subunit	A1+A2+B	6-17	Illnesses of stomach & intestines	5 months	4	930	4	905
Elshina 2000	Polymer subunit	A1+A2+B	6-17	Skin diseases	5 months	6	930	2	905
Elshina 2000	Polymer subunit	A1+A2+B	6-17	Allergies	5 months	3	930	3	905
Elshina 2000	Polymer subunit	A1+A2+B	6-17	Cardiovascular illnessess	5 months	5	930	3	905

Table 15. Inactivated vaccine safety, cohort studies, > 1 dose

Study reference	Vaccine type	Influenza type	Age group (years)	Outcome	Follow up (days)	n treatment	N treatment	n control	N control
2 doses									

Table 15. Inactivated vaccine safety, cohort studies, > 1 dose (*Continued*)

Vasilyeva 1988 II	Whole	A1+A2	11-14	Temperature 37.0-37.5°C	5	18	133	8	109
Vasilyeva 1988 II	Whole	A1+A2	11-14	Temperature >= 37.6°C prob to 38.5°C	5	2	133	0	109
Vasilyeva 1988 II	Whole	A1+A2	11-14	Hyperemia <= 25mm	5	111	133	11	109
Vasilyeva 1988 II	Whole	A1+A2	11-14	Hyperemia >= 26mm	5	7	133	0	109
Vasilyeva 1988 II	Whole	A1+A2	11-14	Infiltration <= 25mm	5	43	133	1	109
Vasilyeva 1988 II	Whole	A1+A2	11-14	Infiltration >= 26mm	5	1	133	0	109
Vasilyeva 1988 II	Whole	A1+A2	11-14	Intoxication & catarrh in nasopharynx	5	12	133	1	109
Vasilyeva 1988 II	Whole	A1+A2	11-14	Pain at administration site	5	7	133	0	109
Vasilyeva 1988 II	Whole	A1+A2	11-14	Request urgent medical attention	30	7	2420	2	1243
Vasilyeva 1988 II	Whole	A1+A2	11-14	Hospitalisation	30	1	2420	0	1243
Vasilyeva 1988 II	Whole	A1+A2	11-14	Morbidity of all nosological forms (except influenza and ARI)	6 months	58	2420	46	1243

Table 15. Inactivated vaccine safety, cohort studies, > 1 dose (*Continued*)

2 doses over 2 years									
Vasilyeva 1988 II	Whole	A1+A2	11-14	Temperature 37.0-37.5°C	5	12	145	4	136
Vasilyeva 1988 II	Whole	A1+A2	11-14	Temperature >= 37.6°C prob to 38.5°C	5	1	145	0	136
Vasilyeva 1988 II	Whole	A1+A2	11-14	Hyperemia <= 25mm	5	122	145	1	136
Vasilyeva 1988 II	Whole	A1+A2	11-14	Hyperemia >= 26mm	5	0	145	0	136
Vasilyeva 1988 II	Whole	A1+A2	11-14	Infiltration <= 25mm	5	40	145	0	136
Vasilyeva 1988 II	Whole	A1+A2	11-14	Infiltration >= 26mm	5	0	145	0	136
Vasilyeva 1988 II	Whole	A1+A2	11-14	Intoxication & catarrh in nasopharynx	5	13	145	0	136
Vasilyeva 1988 II	Whole	A1+A2	11-14	Pain at administration site	5	6	145	0	136
3 doses									
Vasilyeva 1988 II	Whole	A1+A2	11-14	Temperature 37.0-37.5°C	5	12	183	11	176

Table 15. Inactivated vaccine safety, cohort studies, > 1 dose (*Continued*)

Vasilyeva 1988 II	Whole	A1+A2	11-14	Temperature >= 37.6°C prob to 38.5°C	5	4	183	2	176
Vasilyeva 1988 II	Whole	A1+A2	11-14	Hyperemia <= 25mm	5	132	183	12	176
Vasilyeva 1988 II	Whole	A1+A2	11-14	Hyperemia >= 26mm	5	17	183	0	176
Vasilyeva 1988 II	Whole	A1+A2	11-14	Infiltration <= 25mm	5	69	183	0	176
Vasilyeva 1988 II	Whole	A1+A2	11-14	Infiltration >= 26mm	5	2	183	0	176
Vasilyeva 1988 II	Whole	A1+A2	11-14	Intoxication & catarrh in nasopharynx	5	6	183	7	176
Vasilyeva 1988 II	Whole	A1+A2	11-14	Pain at administration site	5	3	183	1	176
Vasilyeva 1988 II	Whole	A1+A2	11-14	Morbidity of all nosological forms (except influenza and ARI)	6 months	20	183	13	176
3 doses over 2 years									
Vasilyeva 1988 II	Whole	A1+A2	11-14	Temperature 37.0-37.5°C	5	36	95	28	95

Table 15. Inactivated vaccine safety, cohort studies, > 1 dose (*Continued*)

Vasilyeva 1988 II	Whole	A1+A2	11-14	Temperature >= 37.6°C prob to 38.5°C	5	1	95	3	95
Vasilyeva 1988 II	Whole	A1+A2	11-14	Hyperemia <= 25mm	5	73	95	0	95
Vasilyeva 1988 II	Whole	A1+A2	11-14	Hyperemia >= 26mm	5	12	95	1	95
Vasilyeva 1988 II	Whole	A1+A2	11-14	Infiltration <= 25mm	5	10	95	0	95
Vasilyeva 1988 II	Whole	A1+A2	11-14	Infiltration >= 26mm	5	0	95	0	95
Vasilyeva 1988 II	Whole	A1+A2	11-14	Intoxication & catarrh in nasopharynx	5	8	95	5	95
Vasilyeva 1988 II	Whole	A1+A2	11-14	Pain at administration site	5	11	95	1	95
4 doses									
Vasilyeva 1988 II	Whole	A1+A2	11-14	Temperature 37.0-37.5°C	5	17	54	11	65
Vasilyeva 1988 II	Whole	A1+A2	11-14	Temperature >= 37.6°C prob to 38.5°C	5	1	54	0	65
Vasilyeva 1988 II	Whole	A1+A2	11-14	Hyperemia <= 25mm	5	44	54	0	65

Table 15. Inactivated vaccine safety, cohort studies, > 1 dose (*Continued*)

Vasilyeva 1988 II	Whole	A1+A2	11-14	Hyperemia >= 26mm	5	4	54	0	65
Vasilyeva 1988 II	Whole	A1+A2	11-14	Infiltration <= 25mm	5	6	54	0	65
Vasilyeva 1988 II	Whole	A1+A2	11-14	Infiltration >= 26mm	5	1	54	0	65
Vasilyeva 1988 II	Whole	A1+A2	11-14	Intoxication & catarrh in nasopharynx	5	6	54	4	65
Vasilyeva 1988 II	Whole	A1+A2	11-14	Pain at administration site	5	6	54	0	65
Vasilyeva 1988 II	Whole	A1+A2	11-14	Morbidity of all nosological forms (except influenza and ARI)	6 months	3	107	3	114

The data for all temperature outcomes in RCTs of inactivated vaccine is presented in additional Table 16. Local reactions are shown in Table 17 and all other short term reactions in Table 12.

Table 16. Live vaccine safety, cohort studies

Study reference	Influenza types	Doses	Age group (years)	Outcomes	Follow up (days)	n treatment	N treatment	n control	N control
Slepushkin 1994 a	A1+A2	2	7-14	Temperature 37.6-38.5°C	Unspecified	1	162	0*	272*
Slepushkin 1994 b	A1+A2	2	7-14	Temperature 37.6-38.5°C	Unspecified	2	323	2*	278*

Table 16. Live vaccine safety, cohort studies (*Continued*)

Slepushkin 1994 a	A1+A2	2	7-14	Temperature > 38.6°C	Unspecified	0	162	0*	272*
Slepushkin 1994 b	A1+A2	2	7-14	Temperature > 38.6°C	Unspecified	0	323	2*	278*

Table 17. Inactivated vaccine safety, RCTs, one dose, temperature

Reference	Vaccine type	Influenza types	Age group (years)	Temperature range	Follow up (days)	n treatment	N treatment	n placebo	N placebo
Up to 38°C									
Gutman 1977	Whole	A1	3-6	<= 38°C	1	0	10	0	12
Gutman 1977	Split	A1	3-6	<= 38°C	1	3	24	0	12
Gutman 1977	Whole	A1	6-10	<= 38°C	1	0	24	0	6
Gutman 1977	Split	A1	6-10	<= 38°C	1	0	40	0	6
Slepushkin 1991	Whole ?	A2	8-15	37.1-37.5°C	? 4/5	2	56	1	44
Khan 1996	Split	A1+A2+B	9-12	37.5-37.9°C*	4	1	168	1	87
Khan 1996	Split	A1+A2+B	9-12	37-37.4°C*	4	15	168	0	87
Vasil'eva 1988 I	Whole	A1+A2	11-14	30-37.5°	5	15	85	10	86
Vasil'eva 1988 I	Whole	A1+A2	11-14	30-37.5°	5	17	87	10	86
Vasil'eva 1988 I	Whole	A1+A2	11-14	30-37.5°	5	47	270	45	252

Table 17. Inactivated vaccine safety, RCTs, one dose, temperature (*Continued*)

Under to over 38°C [range 37.6-39.4°C]									
Wright 1976	Whole ?	B	12-28 months	37.8-38.8°C	<12 hr	2	16	1	19
Levine 1977	Split1	A1	3-5	<= 37.8°C	1	0	4	3	33
Levine 1977	Split2	A1	3-5	<= 37.8°C	1	2	16	3	33
Levine 1977	Split3	A1	3-5	<= 37.8°C	1	0	5	3	33
Levine 1977	Split4	A1	3-5	<= 37.8°C	1	0	4	3	33
Levine 1977	Split5	A1	3-5	<= 37.8°C	1	0	14	3	33
Levine 1977	Split6	A1	3-5	<= 37.8°C	1	0	5	3	33
Levine 1977	Whole1	A1	3-5	<= 37.8°C	1	4	22	3	33
Levine 1977	Whole2	A1	3-5	<= 37.8°C	1	5	22	3	33
Levine 1977	Whole3	A1	3-5	<= 37.8°C	1	10	22	3	33
Levine 1977	Whole4	A1	3-5	<= 37.8°C	1	2	13	3	33
Wright 1976	Whole ?	B	3-6	37.8-38.8°C	2	9	29	0	4
Vasil'eva 1982	Whole ?	A2	7-10*	37.6-38.5°C	5	1	70	1	44
Vasil'eva 1982	Whole ?	A2	7-10*	37.6-38.5°C	5	1	43	0	38

Table 17. Inactivated vaccine safety, RCTs, one dose, temperature (*Continued*)

Beutner 1979	Whole ?	A2	7-14	37.8-39.4°C	7	39	300	3	275
Slepushkin 1991	Whole ?	A2	8-15	<= 37.6°C	? 4/5	0	56	0	44
Vasilyeva 1988 I	Whole	A1+A2	11-14	37.6-38.5°C	5	1	85	0	86
Vasilyeva 1988 I	Whole	A1+A2	11-14	37.6-38.5°C	5	0	87	0	86
Vasilyeva 1988 i	Whole	A1+A2	11-14	37.6-38.5°C	5	9	270	1	252
Over 38°C									
Gutman 1977	Whole	A1	3-6	38.1-38.5°C	1	0	10	0	12
Gutman 1977	Split	A1	3-6	38.1-38.5°C	1	0	24	0	12
Gutman 1977	Whole	A1	6-10	38.1-38.5°C	1	1	24	0	6
Gutman 1977	Split	A1	6-10	38.1-38.5°C	1	0	40	0	6
Over 38.5°C									
Wright 1976	Whole ?	B	12-28 months	38.9-39.9°C	<12 hr	7	16	1	19
Gutman 1977	Whole	A1	3-6	38.6-39°C	1	0	10	0	12
Gutman 1977	Split	A1	3-6	38.6-39°C	1	0	24	0	12
Wright 1976	Whole ?	B	3-6	38.9-39.9°C	2	2	29	2	4
Gutman 1977	Whole	A1	6-10	38.6-39°C	1	1	24	0	6

Table 17. Inactivated vaccine safety, RCTs, one dose, temperature (*Continued*)

Gutman 1977	Split	A1	6-10	38.6-39°C	1	0	40	0	6
Vasil'eva 1988 I	Whole	A1+A2	11-14	> 38.5°C	5	0	85	0	86
Vasil'eva 1988 I	Whole	A1+A2	11-14	> 38.5°C	5	0	87	0	86
Vasil'eva 1988 I	Whole	A1+A2	11-14	> 38.5°C	5	0	270	0	252
Over 40°C									
Wright 1976	Whole ?	B	12-28 months	40.0-40.5°C	<12 hr	2	16	0	19
Wright 1976	Whole ?	B	3-6	40.0-40.5°C	2	0	29	0	4
Wright 1976	Whole ?	A2	7-14	>= 40°C	7	0	300	0	275
Unspecified temperature									
Wright 1976	Whole ?	B	12-28 months	Felt hot	2	0	16	0	19
Wright 1976	Whole ?	B	3-6 years	Felt hot	2	2	29	0	4

One RCT, Vasil'eva 1988a (15 outcomes) and two cohort studies, El'shina 2000 (six outcomes) and Vasil'eva 1988b (one outcome) included safety outcomes data up to six months after inoculation. The long term outcome data for all inactivated vaccine trials is presented in additional Table 18.

Table 18. Inactivated vaccine safety, RCTs, one dose, other short-term outcomes

Study reference	Vaccine type	Influenza types	Age group (years)	Outcome	Follow up	n treatment	N treatment	n control	N control
Up to 7 days									
Gutman 1977	Whole	A1	3-6	Headache	1 day	0	10	0	12
Gutman 1977	Split	A1	3-6	Headache	1 day	0	24	0	12
Gutman 1977	Whole	A1	6-10	Headache	1 day	2	24	0	6
Gutman 1977	Split	A1	6-10	Headache	1 day	2	40	0	6
Elshina 2000	Polymer subunit	A1+A2+B	6-14	Headache	5 days	1	40	1	40
Beutner 1979	Whole?	A2	7-14	Headache	7 days	51	300	22	275
Slepushkin 1991	Whole?	A2	8-15	Headache	? 4/5 days	1	56	1	44
Elshina 2000	Polymer subunit	A1+A+B	14-17	Headache	5 days	4	30	6	30
Wright 1976	Whole?	B	12-28 months	Malaise/ listlessness	2 days	7	16	0	19
Levine 1977	Split	A1	3-5	Malaise	1 day	0	4	0	33
Levine 1977	Split	A1	3-5	Malaise	1 day	0	16	0	33
Levine 1977	Split	A1	3-5	Malaise	1 day	0	5	0	33
Levine 1977	Split	A1	3-5	Malaise	1 day	0	4	0	33
Levine 1977	Split	A1	3-5	Malaise	1 day	0	14	0	33

Table 18. Inactivated vaccine safety, RCTs, one dose, other short-term outcomes (*Continued*)

Levine 1977	Split	A1	3-5	Malaise	1 day	0	5	0	33
Levine 1977	Whole	A1	3-5	Malaise	1 day	0	22	0	33
Levine 1977	Whole	A1	3-5	Malaise	1 day	0	22	0	33
Levine 1977	Whole	A1	3-5	Malaise	1 day	4	22	0	33
Levine 1977	Whole	A1	3-5	Malaise	1 day	0	13	0	33
Wright 1976	Whole?	B	3-6	Malaise/ listlessness	2 days	2	29	0	4
Gutman 1977	Whole	A1	3-6	Malaise	1 day	0	10	0	12
Gutman 1977	Split	A1	3-6	Malaise	1 day	0	24	0	12
Gutman 1977	Whole	A1	6-10	Malaise	1 day	2	24	0	6
Gutman 1977	Split	A1	6-10	Malaise	1 day	2	40	0	6
Levine 1977	Split	A1	3-5	Nausea	1 day	0	4	0	33
Levine 1977	Split	A1	3-5	Nausea	1 day	0	16	0	33
Levine 1977	Split	A1	3-5	Nausea	1 day	0	5	0	33
Levine 1977	Split	A1	3-5	Nausea	1 day	0	4	0	33
Levine 1977	Split	A1	3-5	Nausea	1 day	0	14	0	33
Levine 1977	Split	A1	3-5	Nausea	1 day	0	5	0	33
Levine 1977	Whole	A1	3-5	Nausea	1 day	0	22	0	33

Table 18. Inactivated vaccine safety, RCTs, one dose, other short-term outcomes (*Continued*)

Levine 1977	Whole	A1	3-5	Nausea	1 day	1	22	0	33
Levine 1977	Whole	A1	3-5	Nausea	1 day	0	22	0	33
Levine 1977	Whole	A1	3-5	Nausea	1 day	0	13	0	33
Beutner 1979	Whole?	A2	7-14	Nausea, vomiting	7 days	18	300	17	275
Gutman 1977	Whole	A1	3-6	Stomach ache	1 day	0	10	0	12
Gutman 1977	Split	A1	3-6	Stomach ache	1 day	0	24	0	12
Gutman 1977	Whole	A1	6-10	Stomach ache	1 day	0	24	0	12
Gutman 1977	Split	A1	6-10	Stomach ache	1 day	1	40	0	6
Elshina 2000	Polymer subunit	A1+A2+B	6-14	Sore throat	5 days	1	40	0	40
Slepushkin 1991	Whole?	A2	8-15	Sore throat	? 4/5 days	0	56	0	44
Elshina 2000	Polymer subunit	A1+A2+B	14-17	Sore throat	5 days	3	30	2	30
Elshina 2000	Polymer subunit	A1+A2+B	6-14	Cough	5 days	1	40	0	40
Slepushkin 1991	Whole?	A2	8-15	Cough	? 4/5 days	0	56	1	44
Elshina 2000	Polymer subunit	A1+A2+B	14-17	Cough	5 days	1	30	2	30
Elshina 2000	Polymer subunit	A1+A2+B	6-14	Head cold	5 days	1	40	1	40
Slepushkin 1991	Whole?	A2	8-15	Head cold	? 4/5 days	0	56	0	44
Elshina 2000	Polymer subunit	A1+A2+B	14-17	Head cold	5 days	0	30	2	30

Table 18. Inactivated vaccine safety, RCTs, one dose, other short-term outcomes (*Continued*)

Elshina 2000	Polymer subunit	A1+A2+B	14-17	Feeling unwell	5 days	5	30	3	30
Beutner 1979	Whole?	A2	7-14	Soreness, aching, chills	7 days	42	300	0	275
Wright 1976	Whole?	B	3-6	School absence	2 days	3	29	0	4

In 2005 we reported that in spite of the large amount of data available, particularly for temperature reactions, we could not carry out meta-analysis for any outcome because of the heterogeneity in the presentation of outcomes in the included studies. Additional Table 4 and Table 16 showed the number of different categories of temperature ranges used, the variability in lengths of follow up period and age-group distribution making any meaningful analysis impossible. All the extracted safety data were, however, presented in additional tables 01 to 13. In 2007 the situation has not changed.

The case control study assessing safety of 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 ICD categories and then using Vaccine Safety Datalink (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.

This kind of data mining is not likely to clarify the safety profile of TIV.

Twenty-seven letters or e-mails were written to vaccine manufacturers requesting any additional, unpublished, information they may have on influenza vaccines, particularly long-term safety data. Each manufacturer on the WHO influenza vaccine manufacturers web page was contacted. We received three responses (one covering three of the contacted companies who were part of the same multinational) saying that there was no additional data, one response saying that the company ceased making flu vaccines in 1994 and four letters were returned to us by national postal services as companies no longer existed. Any information collected on vaccine manufacturers and change of addresses was passed on to WHO.

We wrote to 15 first or corresponding authors or research group leaders of the 31 studies (30 RCTs and one cohort study) included in our review to enquire about any unpublished data. Some authors had published more than one study, and e-mail addresses for two authors of four studies (one RCT and three cohort studies) could not be found. We received 12 replies (80% response rate), accounting for 27 (87%) of the studies included in our review.

One corresponding author was contacted to ask for unpublished safety outcome data, which from the methods and results of the paper had obviously been recorded but not published (the outcomes were not significantly associated with either increased or decreased risk in vaccine recipients) (Bergen 2004). The authors were unable to release the data to us without the sponsor's authorisation. The sponsor declined. We reported the failure to release this safety data in a letter to the Lancet in September 2005 (Jefferson 2005a). We decided to exclude this study from the review rather than knowingly include a paper containing bias in its presentation of outcomes. In addition, two other RCTs (three data sets) of the live attenuated vaccine included in the 2007 update show major inconsistencies in the reporting of safety denominators (Tam 2007; Vesikari 2006a; Vesikari 2006b)

DISCUSSION

Our review shows that live attenuated influenza vaccines have good efficacy (up to 82%) but lower effectiveness (around 33%) in children aged more than two years. Attenuated vaccines may be effective in controlling a school outbreak, although this observation is based on an old, poorly reported Russian study (Slepushkin 1974). Live attenuated vaccines are not licensed for use in children aged below two years.

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). Their effectiveness is around 28% for children aged more than two, but we could find no evidence on children aged two years or below. Our conclusions on inactivated vaccines are based on more than 15,000 observations from randomised studies.

Evidence from cohort studies (9213 observations) yield less conservative estimates suggesting that inactivated vaccines have higher (up to 64%) efficacy and effectiveness (56%) in the over six years age group, but in children aged less than two, their efficacy is no better than that of a placebo and there is no evidence of their effectiveness.

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 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 (Colombo 2001; Khan 1996) and a third trial showing a mean absence reduction of four days (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 (Vesikari 2006a). Evidence for other outcomes (secondary cases, lower respiratory tract disease, drug prescriptions, AOM and its consequences, and socio-economic 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 AOM. Virosomal vaccines reduce antibiotic consumption, school and work absenteeism but these observations are based on a single cohort study at high risk of bias (Salleras 2006).

Our review includes eighteen papers of seventeen studies translated from Russian. To our knowledge, the Russian studies have not as yet been included in a discussion of this topic.

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 difference 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 declines), 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 circulating viral 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.

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 goodness of fit between vaccines used in the studies, circulating strain 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 2007). 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.

We found a large data set showing good quality evidence of vaccines' efficacy in children aged two years or more, with a bias in favour of two-dose live attenuated vaccines. As we had already observed in our Cochrane review of influenza vaccines in healthy adults, there is marked difference between the efficacy and effectiveness of the vaccines due to the large proportion of ILIs ('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 and community transmission of influenza.

We were astonished to find only one safety study of inactivated vaccine in children under two years carried out nearly 30 years ago in 35 children (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.

The range and diversity of safety outcomes found in the included studies 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 (http://www.brightoncollaboration.org/internet/en/index/definition˙˙˙guidelines.html) on the recording and presentation of temperature and induration, with guidelines on more outcomes in the pipeline. The results of this search and review clearly show the need for the existence of such guidelines and their adoption by researchers worldwide.

AUTHORS' CONCLUSIONS

Implications for practice

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

Implications for research

More randomised trials are required to test the efficacy of influenza vaccines, particularly of inactivated vaccine, 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*

CHARACTERISTICS OF STUDIES

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

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 and 8 to 15. 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
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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Alexandrova 1986

Methods	C-RCT possibly followed by two cohort studies
Participants	'Nearly 30,000 school children (aged 7 -15) and preschool children (aged 3 - 6). The units sampled were schools and kindergartens. The samples were preformed using random sampling numbers and stratified sampling in schools with different number of children. Initially reactogenicity of the vaccine was studied on a limited group of school children (190) and children between 3 and 6 (267). After the low reactogenicity of the vaccine was assessed, vaccination of large groups of children was undertaken. The trial was extended to 45 school (in 26 the bivaccine was administered, in 19 placebo) and to 142 preschool community (the children of 76 received vaccine , those from the others 66 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 group of study population, who were vaccinated in October 1982, a reactogenicity study was separately carried out. This group consisted of 457 pupils and children , who were divided in two groups. One group were given vaccine, the other received placebo. Cases of mild, moderate or febrile reaction within five 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.

Alexandrova 1986 (*Continued*)

Outcomes	1. 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 divaccine 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:"The data on morbidity from acute respiratory diseases and tonsillitis for 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 for both groups ; for the more susceptible age group of 3-6 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."
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 I have classified it as C-RCT. There appears to be an extension of the safety data to 14228 placebo and 157272 vaccine recipients. 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

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Allison 2006

Methods	5-practice retrospective cohort study taking place in Colorado during the 2003-2004 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 - 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 two peaks of ILI attendances one 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 participant in fully vaccinated (FV), partially vaccinated (PV) or unvaccinated (UV) but as some UV became PVs and FVs as the season progressed denominators are unstable. In addition FV include those that had one 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
Interventions	1 and 2 dose vaccinations vs do-nothing. The vaccine must have been TIV which is the only one registered in this age group in the US. No mentions 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
Notes	The authors conclude that "a total of 28% of the patients had an ILI office visit, and 5% had a pneumonia/influenza visit. Hazard ratios (HRs) for FV versus UV were 0.31 (95% confidence interval [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 2003-2004 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 randomized controlled trial of registry-based reminder recall in 5 private pediatric practices in Denver, Colorado from September 1, 2003 through February 29, 2004 (18. Kempe A, Daley MF, Barrow J, Allred N, Hester N, Beaty BL, et al. Implementation of universal influenza immunization recommendations for healthy young children: results of a randomized, 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

Item	Authors' judgement	Description

Allison 2006 (*Continued*)

Allocation concealment?	Unclear	D - Not used

Anonymous 2005

Methods	Case-control study based on the 45 British Columbia surveillance system sites in which for the 2004-2005 sentinel physicians were encouraged to do take more swabs. Cases were subjects who reported to sentinel physicians with acute onset respiratory illness with fever and cough and one 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 2004-2005 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 standardized 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
Notes	The authors conclude that" We found age-adjusted point estimates for VE against medical consultation for laboratory-confirmed influenza A during the mismatched 2004-2005 season to range as low as 40% and as high as 75%. VE varied with age, definition of immunization status and whether analysis was restricted to presentation within 48 hours of ILI onset. Overall, our estimates suggest cross-protection for the 2004-2005 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 2004-2005 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

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	D - Not used

Bashliaeva 1986

Methods	Placebo-controlled cohort study (does not state whether children were randomly assigned to groups following division by age and school conditions)carried out in two regions of the then USSR during the 1983-1984 season among schoolchildren. The trial was carried out in 106 schools in the Sverdlovsk and Babushkinskii regions of Moscow. Participants were divided into four groups. The authors report that they were "equal in number, age and conditions in the childrens' schools". There were two active arms and two control arms. The 1983-84 is described at length but not clearly. It would appear that there was circulation of H1N1, H2N3 and B viruses- It would appear the vaccines were not well-matched to any of these, especially the B virus. Table 1 reports serological responses, Table 2 reports incidence of ILI cases and Table 3 influenza cases
Participants	2274 children were inoculated once with the two types of the vaccine, 876 were inoculated twice; 1321 and 573 children were inoculated with placebo respectively
Interventions	Two 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 mkg (Type 15) and 29.2 mkg (Type 16). The vaccines also contained ovalbumin (Type 15 was 0.125 mkg/ml, in Type 16 it was 0.06 mkg/ml). Sterile, apyrogenic, physiological solution was used for placebo. Vaccines or placebo were administered subcutaneously; two doses of 0.5 ml, with an interval of 28-30 days
Outcomes	Effectiveness Influenza and ILI. There are two 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- 18-20 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 two 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 injection". The reasons for his apparent attrition are unclear. Safety See above. Other harms data (headaches etc are reported as one-liner with no data
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 he 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

Bashliaeva 1986 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	D - Not used

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 - rhinorrhea on 2 consecutive days; lower respiratory illness - wheeze or pneumonia; otitis media Viral shedding (data not extracted) Serologic response to vaccine (data not extracted)
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

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	D - Not used

Belshe 1998

Methods	Multicenter, prospective, randomised, double blind, placebo-controlled multicenter trial to assess efficacy and safety of a cold-adapted influenza vaccine in single and two dose regime vs 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 one-dose. No statistical differences in age, sex, race, day-care se and household makeup were observed between vaccine and placebo groups. Subjects scheduled to receive two 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 one-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 re-assortants 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 (1996-97). - 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 one-dose group 189 subjects were vaccinated and 89 received placebo; in the two-dose group 881 subjects were randomised to receive vaccine and 433 to receive placebo. From this group 42 subjects 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 two 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. One 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 two groups together.
Outcomes	Serological Hemagglutination Inhibiting Antibody Responses After one or two 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 otitis media, 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

Belshe 1998 (*Continued*)

	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.
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

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Belshe 2000a

Methods	See Belshe 1998
Participants	1358 healthy children who previously participated in year 1 of trial (Belshe 1998). Aged 26 to 85 months
Interventions	Revaccination with live attenuated, cold-adapted trivalent (H1N1, H2N3 & 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, otitis media 6. Serious adverse events occurring at any time during the study 7. Incidences of flu-like illness detected by surveillance
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

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 one 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 one 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 two epidemics. The first of these lasted between med 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 (one, 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 "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 one to four weeks after vaccination. Data about local (pain-tenderness, erythema , swelling , none) and systemic reactions (Headache, nausea-vomiting, soreness-aching-chills, none sr) are reported"
Notes	"The authors conclude that both vaccines work as well as the bivalent."

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Beutner 1979b

Methods	See Beutner 1979a
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

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 finf 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 two 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 - Four groups of children received 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-Feb 88. Determined by 4-fold increase in antibodies from subsamples 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

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 mkg 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 2. (excluding confirmed influenza B diagnosis)i.e. during influenza A(H3N2) outbreak period 3. Cases of laboratory confirmed influenza (H3N2) in school 2 between 16/1/88 and 15/2/88 4. (excluding confirmed influenza B diagnosis) 5. Re isolation of virus (not for data extraction) 6. Rise in antibody titre in children inoculated with vaccine strain A/47/S in year 2 (not for data extraction) 7. Slight increase in temperature (not extractable - no placebo data given) 8. Subjective events (not extractable - no placebo data given)
Notes	The authors conclude that BIV 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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

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 one month after second dose. So desirable that vaccination should be completed no later than one 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

Chumakov 1987 (*Continued*)

Interventions	See Bashliaeva 1986
Outcomes	Cases of ARI and influenza
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Clover 1991

Methods	Multicenter , cluster randomised, placebo controlled clinical trial in which the efficacy of bivalent cold adapted and trivalent inactivated influenza vaccines were compared. Seventy percent of the study population was already been immunised in the previous "Gruber 90", whose subjects were enrolled at the same centers 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	A hundred three 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 one of the two 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 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. One dose intranasally administered. - Trivalent, inactivated influenza vaccine (standard licensed Fluogen, Parke Davis, Detroit) containing 15 ?g of each A/Chile/83 H1N1, A/Missisipi/85 (H3N2) and B/Ann Arbor/86 hemagglutinin antigen in 0,5 ml. One 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 the 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

Clover 1991 (*Continued*)

	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 characterized by review of records which included date of onset, symptoms, physical signs diagnosis of each contact." Safety N/A
Notes	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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

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 never been immunised against influenza. Children with hypersensitivity reactions to eggs were excluded. Of the 398 meeting the inclusion criteria, 344 accepted to participate. One hundred seventy seven 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. Two doses one month apart were administered. Subjects immunisation took place between October 15 and November 15 , 1995. - No treatment.
Outcomes	Serological Paired sera for in 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 subjects 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 day care absenteeism (also for the family members). Influenza-like illness was defined as rectal temperature above 38,%°C and cough or sore throat lasting at least 72 hours." Safety

Colombo 2001 (*Continued*)

	"Systemic reactions (fever) Local reactions (erythema at the injection site) Parent were asked to contact the paediatrician in case of adverse event"
Notes	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 was in a day care center.- 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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Desheva 2002

Methods	RCT of adult variant (single dose) of live influenza vaccine in children aged 3 to 6 years. 2 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 1999-2000 - 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 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 sub-group prior to inoculation and 21 days after and analysed for haemagglutinin inhibition Effectiveness ILI, bronchitis infections, somatic illness and allergic pathologies (the last two are difficult to understand and have not been extracted Safety Fever (in different temp breakdowns), headache and catarrhal symptoms

Desheva 2002 (*Continued*)

Notes	Notes The authors conclude that the vaccine is safe and effective. I 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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

El'shina 2000

Methods	Report of a two-phase pilot randomised controlled trial carried out in 1997-1998 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
Participants	In the first study two groups (aged 14-17 years) were formed by randomisation. Both groups had 30 participants. In the second study 40 children aged 6-14 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 two 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 unvaccinated 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

El'shina 2000 (*Continued*)

	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"
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 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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Fujieda 2006

Methods	Prospective cohort study carried out in 54 clinics around Japan during the 02-03 season. The study assessed the effectiveness of TIV against ILI. Baseline questionnaires were filled in at enrolment and then an "attack" (Banzai!) questionnaire in which every week for 17 weeks parents recorded children's body temperature in 3 steps of 1 degree Centigrade. There authors report ILI surveillance Japan-wide with peak isolates of A and B viruses in Jan-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 one or two 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 between 38 and 39 and 39 or more (but no description of how temp was taken by parents or whether follow-up was complete) Safety N/A

Fujieda 2006 (*Continued*)

Notes	The authors conclude that The adjusted odds ratio (OR) and its 95% confidence interval (95% CI) were calculated by the proportional odds model using logistic regression with three-level outcome variables (< 38.0/38.0-38.9/> or =39.0 degrees C). A significantly decreased OR of vaccination was observed (OR: 0.76; 95% CI: 0.66-0.88), corresponding to a vaccine effectiveness (1-OR) of 24% (95% CI: 12%-34%). When the analysis was confined to those aged > or =2 years, a more pronounced OR (0.67, 0.56-0.79) was obtained with a vaccine effectiveness of 33% (21%-44%). On the other hand, no significant vaccine effectiveness was detected among very young children; the ORs were 1.84 (0.81-4.19)for those <1 year of age and 0.99 (0.72-1.36)for those 1.0-1.9 years of age and 1.07 (0.80-1.44)when these two 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 these non random sampling is generalisable up to 97% of ILIs were not due to influenza

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Goodman 2006

Methods	Industry funded case-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 two "seasons": 2002-03 and 2003-04. There is no declaration of conflicts of interest of the authors. Cases: healthy children aged 6-23 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	13383 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 one-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 one 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 to 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 0-42)

Goodman 2006 (*Continued*)

	White blood cell disorders 0-42 Rheumatic diseases 0-42 Nephrotic syndromes 0-42 Alopecia 0-42 Urticaria 0-3 Muscle weakness 0-42 Myalgia 0-42 Neuralgia 0-42 Seizures 0-42 Polyarteritis 0-42 Myoglobinuria 0-42
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. One liner by-the- by effectiveness assessment of vaccine. Multivariate modelling use is unclear. How can you adjust for 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

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	D - Not used

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 1991-1992 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, 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

Grigor'eva 1994 (*Continued*)

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 two 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 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
Notes	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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

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 one individual. The vaccine and placebo were administered as coded preparations. The influenza epidemic of the 1999-2000 season was caused by the influenza virus type A/Sydney/5/97 (H3N2)
Participants	2486 healthy children aged between 7-14 years during the 1999-2000 season
Interventions	Children's and the 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

Grigor'eva 2002 (*Continued*)

	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
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

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Gruber 1990

Methods	Multicenter 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 one of three immunisation groups : thirty percent 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). Unvaccinated 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 two 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/

Gruber 1990 (*Continued*)

	6/83 (H1N1) and A/Korea/1/82 (H3N2). One dose of 0,5 ml intranasally administered. Or 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. One dose of 0,5 ml intramuscularly administered Or 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 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.
Notes	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 utilizable for the analysis. 4) It is impossible to state how many subjects received placebo intranasally and how many received it intramuscularly. This don't permit to analyse 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

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Gruber 1996

Methods	Multicenter, 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 - 18 months who were enrolled at some vaccination units : Baylor College of Medicine, St. Louis University, University of Rochester, Vanderbilt University, University of Maryland. One hundred eighty two subjects were vaccinated, all were born after the last influenza A epidemic and had a 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. Vaccine 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 subjects 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. Otitis media was coded separately. A total of 128 illnesses among 181 subjects 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 ten days after vaccination , parents and guardians recorded the subject’s temperature twice a day (morning and evening) and symptoms including cough, rhinorrhea, diarrhea (evening) once a day. Fever was considered any temperature > 37.8°C. For the other symptoms were considered at least 3 stools in 24 h. Parents had to contact the study site if a subject had more than one symptom on a given day or had fever >37.8°C. These were clinically evaluated. Diary information was unavailable for 2 children.”
Notes	The authors conclude that live attenuated vaccines were significantly more effective than inactivated vaccines. Data about epidemic strain isolation in the four arms were pooled based on whether subjects received a H3N2-containing vaccine or not. It is not possible to go back to the isolation in the single four arms.

Risk of bias

Item	Authors’ judgement	Description

Gruber 1996 (*Continued*)

Allocation concealment?	Unclear	D - Not used

Gruber 1997

Methods	Randomised controlled trial, double blind, multicenter 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 - 36 months enrolled from 13 participating institutes on autumn 1993. Subjects were excluded if they had received any vaccine within 3 weeks before vaccination with influenza or placebo.
Interventions	Enrolled subjects were randomised to receive one 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.
Notes	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 clear reported. Data from the table of respiratory symptoms (table 2 of this paper) do not agree with those reported on the table 1 (fever). A total of 1126 study subjects were enrolled but they resulted 1249 from table 1 (and 1123 from table 2).

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	D - Not used

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 group (3 to 6 and 6 to 10 years) and assigned to the preparation by continuous rotation of the vial numbers.

Gutman 1977 (*Continued*)

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 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 Three weeks after vaccination, a serum sample was take 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. Mother 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. Mother registered on a apposite sheet to record 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.
Notes	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 two 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

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Hirota 1992

Methods	Case control study to asses correlation between influenza-like illnesses and influenza immunisation status in schoolchildren aged between 6 and 12 during an epidemic
Participants	Eight hundred fourteen children from one of the nine elementary schools of Kasuga City (Fukoka Prefecture, Japan). Children were aged 6 to 12.

Hirota 1992 (*Continued*)

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 two doses of 0,3 ml. Vaccination was carried out after consensus from parents was obtained : the first dose was on October 25th administered while the second on November 16th 1988. Four hundred ninety six children (60,9%) were not immunised, 187 (23,0%) received two doses of vaccine and 131 (16,1%) only one 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 refers 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), rhinorrhea, 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 subjects 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
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 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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Hoberman 2003a

Methods	Randomised controlled trial to assess effectiveness of inactivated influenza vaccine against Otitis Media and influenza. Two groups in two 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 two 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 Otitis (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 one dose of pneumococcal conjugate vaccine. Within each stratum children were randomised in blocks of 9 by means of a computer generated list to receive two doses of vaccine or placebo in ratio 2:1. The two 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 Vs - Placebo consisting of a standard diluent and supplied also by Aventis. In both years two doses were administered 4 weeks apart. Of the 417 initial subjects, 278 were randomised to receive placebo and 139 to placebo. Five subjects in the vaccine and one in the placebo group were discarded because of failure to meet eligibility criteria. The first dose were administered to 273 (vaccine) and 138 (placebo) children. The second dose were administered to 267 and 134 subjects 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 Vs - Placebo (standard diluent, Aventis) One subject from the placebo group was excluded for failure to reach eligibility. 252 children were administered vaccine, 123 placebo. The second dose were administered to 246 and 118 subjects 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.

Hoberman 2003a (*Continued*)

	-Acute Otitis Media : presence of purulent otorrhea 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 subjects 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 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 (One child had 2 brief episodes of unexplained staring on the day of the first vaccination; one had mild intercostals reactions and wheezing one day after the second vaccination; one child developed acute gastroenteritis 3 days after first vaccination) . Other possible adverse were monitored during the care visits"
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

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Hoberman 2003b

Methods	See Hoberman 2003a
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

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 3-6 years from the PLA in areas not considered at risk and who had not 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 two doses of 0,25 ml administered one 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 one of the following: fever, headache, myalgia or arthralgia, cough, rhinorrhea, sore throat. -Upper respiratory tract symptoms: influenza-like syndrome + common cold." Safety Not assessed. It is reported only that any serious adverse reactions occurred during the study.
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. I have a problem believing that the vaccine protected from the common cold. Viral circulation was not discussed"

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Kawai 2003

Methods	Prospective cohort study carried out during the 2001-2002 in 38 practices in Japan (staffed by participating members of the Japanese Physicians Association. Doctors enrolled consenting vaccinated subjects on an Internet-based register from 1 October to 31 December 2001. Unvaccinated subjects 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

Kawai 2003 (*Continued*)

Participants	Children aged 0 to 15 years (older children participated but from 16 years are not separable from 16 to 64 yrs 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 one, two or no immunisations
Outcomes	Serological Rapid kit testing was carried out in 75 of the 124 subjects 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 subjects in whom they were taken. Effectiveness ILI (sudden onset, temp of 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 unvaccinated arm.
Notes	Notes The authors conclude that the vaccines were 67.6% and 84.5% effective respectively against ILI (one or two immunisations)and 54 and 79.8% against influenza (one or two 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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

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 - 12 years from two 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 subjects were randomly assigned to receive vaccine or placebo, using the route of administration previously chosen by parents or guardians. For this purpose a blocked randomization scheme was used with a vaccine to placebo ratio of 2:1. Vaccines:

Khan 1996 (*Continued*)

	-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 - 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 1990-91 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 were 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 - 17 March 1992, were transcribed from the medical card at the time of serum collection 5 months after vaccination. Absenteeism due to influenza like illness 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 occurred during the official influenza season and is a clinical diagnosis, moreover the employed criteria were not uniform and these outcome 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)
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 two placebos are not reported separately, so it is impossible to assess 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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

King 1998

Methods	Randomised, placebo-controlled multicenter trial.
Participants	Children aged 18 to 71 months in good health. Two hundred thirty eight were altogether enrolled at Baylor College of Medicine Houston, Cincinnati Children Hospital, Saint Louis University and University of Maryland at Baltimore in tree 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 subjects receive vaccine or placebo as drops and the remaining 50 % by spray
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, rhinorrhea, sore throat, or irritability. Children were examined by clinicians if an axillary, oral or rectal temperature > 38°C was observed.
Notes	The authors conclude that the vaccine was safe and immunogenic in 2 of the 3 strains. Small denominator.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

King 2006

Methods	Prospective cohort study carried out 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 in 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 2004-2005 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
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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

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 one dose evaluation of split products, 47 took part in the one dose evaluation of whole virion products and 28 took part in the two dose evaluation of whole virion products

Levine 1977 (*Continued*)

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.
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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

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 5-83 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. Two injection were given subcutaneously 14 days apart. Dosage was on sliding scale per age: children <1 got 0.1 mls, those aged 1 to 6 0.2 mls and those > 6 years 0.3 mls. The comparator was do-nothing as placebo was 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

Maeda 2002 (*Continued*)

Notes	The authors conclude that inactivated influenza vaccine reduces the incidence of influenza A virus infection in children aged 2 to 6 but not in 6-24 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

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Maeda 2004a

Methods	Randomised open controlled trail 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 2.2000/2001 - >15 µg hemagglutinin/0.5 ml A/New Caledonia/20/99 (H1N1), A/Panama/2007/99 and B/Yamanashi/166/98 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
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. A well conducted trial let down by the absence of placebo

Risk of bias

Item	Authors' judgement	Description

Allocation concealment?	Unclear	D - Not used

Maeda 2004b

Methods	See Maeda 2004a
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Maeda 2004c

Methods	See Maeda 2004a
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

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

Nicholls 2004 (*Continued*)

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 US with those vaccinated in the UK, in effect testing the hypothesis of possible lower efficacy of the UK administered vaccine.
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 one or more of cough, sore throat, headache. Outcome were evaluated by questionnaires distributed on 2 April 2002 Safety N/A
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 unvaccinated OR 1.14, 95% CI 0.41 to 3.14). VE was -5% in those vaccinated in 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. I 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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

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 3-15 years old received respectively vaccine or placebo"
Interventions	Enrolled subjects were randomised to receive at least one dose or two doses of live attenuated cold-adapted influenza B vaccine derived by re assortment between wild-type B/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

Obrosova-Serova 1990 (*Continued*)

	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.
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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Ozgur 2006

Methods	Single blind prospective study carried out during the 2003-2004 season in children from 8 day care nurseries around Ankara, Turkey. The study aim was to assess the effectiveness of TIV in preventing acute otitis media (AOM) and otitis media with effusion (OME). Randomisation is not mentioned, comparator is do-nothing, and denominators are uneven. The single blind design refers to the 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 perinfluenza 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 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 unvaccinated, 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 two doses (Fluarix or Vaxigrip). No mentions 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)
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 unvaccinated 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 a 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

Item	Authors' judgement	Description
Allocation concealment?	No	C - Inadequate

Piedra 2002a

Methods	This paper reports the results of two previous trials : Belshe 98 and Belshe 2000. Safety data on vaccination are reported in more detail. The text mentions that some children from the second study year received in the third (epidemic season 1998 - 1999) and fourth study year (1999 - 2000) further doses of cold adapted trivalent influenza vaccine. These groups consisted of 642 and 549 children respectively. Placebo was not administered to the these children.
Participants	For the first and second study year see Belshe 98 and Belshe 2000.
Interventions	First study year (1996-1997): One or two doses of cold adapted trivalent influenza vaccine (containing the strains A/Texas/36/91-like (H1N1), A/Wuhan/359/95-like (H3N2), B/Harbin/7/94-like in egg allantoic fluid) or placebo randomly administered (see Belshe 98). Second study year (1997-1998): One dose of cold adapted trivalent influenza vaccine (strains A/Shenzhen/227/95 - like H1N1 , A/Wuhan/359/95 - like (H3N2) , B/Harbin/7/94 - like in egg allantoic fluid) or placebo randomly administered (see Belshe 2000). - Third and Fourth study year (1998-1999 and 1999-2000): One dose of cold adapted trivalent influenza vaccine (strains A/Beijing/262/95, A/Sydney/5/97, B/Herbin/7/94)
Outcomes	Serological N/A Effectiveness N/A Safety "From Belshe 98: 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. From Piedra 2002: After each dose, parents were asked to record a diary card for 10 days the occurrence of specific symptoms : cough, runny nose or nasal congestion, sore throat , irritability, chills, vomiting, muscle aches, decrease activity, fever, so as to record any symptoms not present in the diary card including drugs. Parents were also contacted by telephone for illness evaluation every 1 to 3 weeks for respiratory illnesses (febrile, afebrile, physician diagnosed otitis media (febrile and afebrile), Physician diagnosed lower respiratory tract illness (it includes croup, bronchitis, pneumonia and wheeze)."

Piedra 2002a (*Continued*)

Notes	The authors conclude that cold adapted trivalent influenza vaccine is safe and well tolerated in children Data for years 3 and 4 not extracted as they are non-comparative. Reporting included a mass of safety data in summary OR faorm which has been transformed but is not very informative. Systemic harms appear to take place within the first 3-4 days. A few serious harms were reported (meningitis but the study committee did not consider them associated with the vaccine. CAIV-T is certainly not without harms.I am concerned about the lack of a do-nothing control arm.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Principi 2003

Methods	Randomised controlled open trial assessing the socio economic 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 URI,LRTI, Drug px and days off school. Not otherwise defined, reported presumably as means and SD Safety N/A
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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

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 hazard ratio (HR), this was used because patients continued to be vaccinated during the influenza season Vaccine efficacy (VE) was calculated as one 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, U.S. 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 fully vaccinated children versus unvaccinated Pneumonia and influenza (P&I) for fully vaccinated versus unvaccinated
Notes	Circulating strain of A (H3N2) Data collected during peak of influenza activity

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

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 one 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 sub-group 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,& * days. 3 criteria used - retention of antigenic specificity, ts-phenotype, localisation of ts-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, Hematological 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. 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, ts-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
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

Rudenko 1988 (*Continued*)

	vaccine content and unclear randomisation and attrition/sampling make the interpretation of the results very difficult

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	No	C - Inadequate

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 subjects) 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 america 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, rhinorrhea, 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)
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Rudenko 1993a

Methods	Two years single blind placebo cluster randomised controlled trial to assess efficacy of both live cold-adapted and inactivated influenza vaccine.
Participants	Children aged 7 - 14 years from 34 schools of Novgorod (URSS). 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 7-10 in the inactivated group received a more highly purified preparation as those aged 11-14. Placebo groups was also divided in two subgroups: one half was administered placebo intranasal 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 1989-1990 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 1990-1991 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 two 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 preparation was antigenically similar to the wild parents present in the live attenuated preparations. For the 7-10 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 3-8 ?g of each component , in the second year 7-10. 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 diagnose 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. To avoid the lack of independence associated with counting multiple illnesses separately, the presence of one or more respiratory illnesses in the epidemic period was counted as one 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

Rudenko 1993a (*Continued*)

	continued through 22.2.1990. The period used to determine frequency of influenza associated illnesses was 1.1. - 4.3.1990. 12837 children received full immunisation in the first year. In the school year 1990 - 1991 the influenza outbreak was cause 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 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 subjects composed these two subgroups. 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 -10). 8 of the 435 children aged 11 - 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 subjects , who received inactivated vaccine (group aged 7 - 10) developed induration so as 17 of 435 in the group aged 11 -14. These data are not extracted as it is unclear how the children were selected"
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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Rudenko 1993b

Methods	See Rudenko 1993a
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Item	Authors' judgement	Description

Rudenko 1993b (*Continued*)

Allocation concealment?	Unclear	D - Not used

Rudenko 1996a

Methods	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 URSS (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 (two doses of 0,5 ml, administered 21 - 28 days apart). Kalinigrad 1986: Intranasal live cold adapted A H1N1 (Virology Department of the Institute of Experimental Medicine, St. Petersburg)Two 0,5 ml doses. Alma Ata 1986 - 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)Two 0,5 ml doses. Alma Ata 1988 - 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)Two 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)Two 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). Two 0,5 ml doses.
Outcomes	Serological "Paired sera tested for seroconversion in sub groups 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 (1986-87 and 1988-89) 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 early 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 - 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 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.

Rudenko 1996a (*Continued*)

	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 adverse events. 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).
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 are not conform to the original randomised arms. Of how many arms consist the Havana trial ? Were vaccination carried out in two years or were all subjects 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 polivaccine 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 7-14 is 18164. From table 7 results that 22.963 recipients received vaccine. Could these two number be erroneously inverted ? (and 4799 of the original 22963 vaccinated excluded). Any subject excluded from the safety analysis of 1988-89 ? 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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Rudenko 1996b

Methods	- Cluster randomised controlled trial - 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 unvaccinated groups and calculating Index of Efficacy using 'generally accepted methods'
Participants	Children aged 3 to 14 years
Interventions	Live recombinant vaccine made from two mono vaccine containing A/47/25/1 (H1N1) and A/47/F (H3N2)

Rudenko 1996b (*Continued*)

Outcomes	Cases of influenza and ARI Safety - 18 categories of somatic illnesses up to 6 months after inoculation
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

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	One 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 38.5C 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
Notes	The authors conclude that "Adjusted vaccination effectiveness was 58.6% (95% CI 49.2 66.3) in preventing acute febrile respiratory illnesses, 75.1% (95% CI 61.0-84.1)in preventing cases of influenza-like illnesses and 88.4% (95% CI 49.2-97.3)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 47.9-65.9)and work-loss of parents (33.3%, 95% CI 8.9-51.2) in children affected by an acute febrile respiratory illness was somewhat lower. Vaccination of children aged 3-14 years in pediatric practices with one dose of virosomal 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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Slepushkin 1974

Methods	Placebo and do-nothing-controlled emergency randomised trial of live attenuated oral influenza vaccine carried out during the 1970-1971 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 (1-3 years) and it appears that this study carried out only ain two arms is the one for which we have data reported in the tables. The vaccine was given 2-3 times with an interval of 10-15 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 "unvaccinated" 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, two 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 1-3 years, 2 ml for children aged 3-7 years and 3 ml for children aged 8-16 years
Outcomes	Serological "In order to determine antibodies, blood serum was taken from those who had been inoculated, before vaccination and between 21-30 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

Slepushkin 1974 (*Continued*)

	- 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"
Notes	The authors conclude that: 1. The establishment of the weak reactogenicity of the Moscow Scientific Research Institute of Virological Preparations' (MNIIVP) live oral influenza substance for children aged 1-3 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, combined with the emergency prophylaxis) increased the efficacy of the live oral influenza vaccine by two 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 1-7 years) and school aged children". The text is so confusing that only the data from the tables have been extracted. However, I am not sure of its relationship with the text

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	No	C - Inadequate

Slepushkin 1988

Methods	Randomised, single blinded placebo-controlled study conducted in a boarding school in Moscow in September to December 1984
Participants	Hundred seven 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. Two doses of 0,5 ml were 28 days administered apart. Vaccine titre was 102 EID50 for the first dose and 107 for the second. Participants were randomly divided to receive vaccine or placebo.

Slepushkin 1988 (*Continued*)

	Fifty eight 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 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."
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 sub-analysis 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

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	D - Not used

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 a 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.
Participants	241 healthy boarding school children aged 8 to 15 years (97, 56, 88 (for CA, BIV 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 BIV (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

Slepushkin 1991 (*Continued*)

	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 (37.1-37.5), local reactions, headache, sore throat, cough, head cold
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 micro neutralization tests. In 69.7% of the children given the inactivated vaccine, seroconversion to the vaccine strain was detected by two 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 temp 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 two doses of CA and 73% (P=0.08) for one dose of BIV. 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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

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 sub-group 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 age 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

Slepushkin 1994 (*Continued*)

	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
Notes	The authors do not draw clear conclusions and it is difficult to understand to 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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

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 immunisation 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 1998-99 & 1999-2000 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 2000-2001' 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 of 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

Slobodniuk 2002a (*Continued*)

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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Slobodniuk 2002b

Methods	See Slobodniuk 2002a
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Slobodniuk 2002c

Methods	See Slobodniuk 2002a
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Item	Authors' judgement	Description

Allocation concealment?	Unclear	D - Not used

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
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 - rhinorrhea, 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)"
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

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	D - Not used

Steinhoff 1991

Methods	"RCT to compare characteristics of two 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 passaging four times 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 virus 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 one 0.5 ml dose (0.25 ml per nostril) Children were observed for 1-2 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 (rhinorrhea, pharyngitis or both) Lower respiratory tract illness (persistent, wheezing or cough) for at least 2 consecutive days Otitis media Children were observed for 1-2 hours daily for 3 days before inoculation and 7 to 9 days after"
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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

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	Twenty two healthy infants and children aged 2-22 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 three 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 vaccines 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 (two 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.
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. Onyl 4 participants were aged less than 6 months

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Tam 2007

Methods	Multicentre (8 centres in Southeast Asia: China, Hong Kong, India, Malaysia, the Philippines, Singapore, Taiwan, and Thailand) randomised controlled trial carried out over three seasons (enrollment 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 randomization 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 enrollment, 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 randomization allocation list. In year 2, randomization 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 randomization list. The per-protocol (PP) population in year 1 included all randomized subjects 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-randomized subjects 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 subjects who were enrolled in the study and received at least 1 dose of study treatment. The year 2 intent-to-treat population included all subjects re-randomized in year 2.
Participants	Starting from 30 September 2000, 3174 children aged 12 to up 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 ration of 2:3. The year 1 PP efficacy population was 2764 subjects (1653 CAIV-T and 1111 placebo). In year 2, 2947 subjects were re-randomized either to a single dose of CAIV-T or placebo from 9 November 2001. The year 2 PP efficacy population was 2527 subjects. 69 subjects from year 1 were not randomized 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. Participants 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 (SD7.4) 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, subjects were randomized 3:2 (CAIV-T: placebo) to receive 2 doses of CAIV-T or 2 doses of placebo at least 28 days apart using a randomization schedule generated by Wyeth. In year 2, subjects were re-randomized 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 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 two). 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 subjects, 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 2000-2001 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 subjects at 5 sites. However "the same subjects 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 subjects 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 subjects 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 medication 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. Serious adverse events (SAEs), including hospitalizations, were monitored from enrollment until the end of the study. Fever, runny nose, decreased activity or appetite and used 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 who was hospitalised with pneumonia 6 days after receiving CAIV-T. The was one 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 usually discrepancies in trials of these CAIV-T vaccines- denominators are reported as ranges with the usual (see Vesikari) caption "†n represents the number of subjects with known values". According to the Table 6, 1345 received CAIVT is season 2 but according to Figure 1 the total should be 1757. There is no mention of the fate of the other children
Notes	The authors conclude that "In year 1, efficacy of CAIV-T compared with placebo was 72.9% [95% confidence interval (CI): 62.8-80.5%] against antigenically similar influenza subtypes, and 70.1% (95% CI: 60.9-77.3%)against any strain. In year 2, revaccination with CAIV-T demonstrated significant efficacy against antigenically similar (84.3%; 95% CI: 70.1-92.4%)and any (64.2%; 95% CI: 54.2-77.3%)influenza strains. In year 1, fever, runny nose/nasal congestion, decreased activity and appetite, and use of fever medication

Tam 2007 (*Continued*)

	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

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Vasil'eva 1982

Methods	Randomised placebo controlled trial of a monovalent injected vaccine in children aged 7-15 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 Temp, induration, headache, malaise, sore throat. Daily physical examinations for 5 days
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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Vasil'eva 1988a

Methods	Randomised controlled trial assessing reactogenicity and immunogenicity of BIV. "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 sub-group. '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)"
Notes	The authors conclude that multiple immunisations with BIV 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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Vasil'eva 1988b

Methods	Randomised placebo-controlled trial carried out during 1983-1984 in the area of Rostov-on-Don in the former USSR. The study was conducted to assess efficacy, effectiveness, safety and immunogenicity of two types of BIV versus placebo. There 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 11-14 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 the January 84 and then a H1N1 epidemic reported in Rost on Don
Participants	13.355 children aged 11-14 and "teenagers" observed of which 9.962 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	BIV 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-0.5 ml").
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 one 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 11-14 years inoculated with the chromatographic preparation contracted influenza and acute respiratory illnesses in February-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 11-14 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

Vasil'eva 1988b (*Continued*)

	received placebo, for the 30 days after immunisation. The total figures for such requests amongst children aged 11-14 years and teenagers were 0.1%-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%-0.06%"" The outcomes reported in this analysis (Table 3) are very unusual (""allergies, bronchitis, neuralgia, carbuncles, stomach ulcers etc) and there is gross imbalance and inconsistencies in the denominators of the arms (centrifugal 6625, adsorptive 491, chromatographic 4655, placebo 3493 =15264)."
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 subcutaneously in a dose of 7.0 mkg of haemagglutinin to school children aged 11-14 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"". I am 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 wicked loss of data. I have trying 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 CDP needs to check). However these numerators do not match even remotely the 198 paired sera taken for influenza diagnosis. Too many inconsistencies."

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Vesikari 2006a

Methods	Double blind randomised controlled trial 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 2000-31 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 up to 35 months attending day-care (at least 12 hours weekly) in one 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 subjects were randomised on 3:2 basis. The 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 6-12 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 one (approx 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 two different strains of influenza B vaccine
Outcomes	Serological Children with fever (rectal 38C or more and oral 37.5 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 one or more of the following: fever (rectal 38C or more and oral 37.5 or more), earache, irritability, diarrhoea, vomiting, otorrhea or any URI symptom. Febrile OM (with fever rectal 38C or more and oral 37.5 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 day care missed by ill children.- At least 1 visit to ER/outpatients department because of ILI. - At least 1 prescription for antibiotics because of ILI. - 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 37.5C, 38.6C and 40C axillary respectively or 38C, 39.1 and 40 rectally). A Es are reported in a mixture of table and text format. I have extracted the A Es 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 subjects 6 to 12 months of age, lower respiratory tract infections reported as serious AEs were pneumonia (2 CAIV-T recipients and 1 placebo recipi- ent), 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

Vesikari 2006a (*Continued*)

	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). Two cases of pneumonia were judged to be possibly, probably, or definitely related to study vaccination. A total of 4 subjects (2 CAIV-T recipients and 2 placebo recipients)were withdrawn from the study because of AEs. No deaths occurred during the study period".
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). Two 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" 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

Item	Authors' judgement	Description
Allocation concealment?	No	C - Inadequate

Vesikari 2006b

Methods	2001-2002 season data from Vesikari 2006
Participants	
Interventions	
Outcomes	
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

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 socio economic class children (80-90% 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%. I 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 one reason or another
Interventions	Cold adapted recombinant spray vaccine (Flumist) in two 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
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; one 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 two designs (before and after comparisons mixed with prospective cohort). High risk of bias

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Wright 1976a

Methods	Two studies are reported in the paper. Randomised controlled trial 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	Thirty three preschool children aged 3 to 6 were enrolled in the other study Thirty five children enrolled in the Paediatric Vaccine Clinic at Vanderbilt Hospital (Nashville, Tennessee) aged between 12 an 28 months.
Interventions	Study subjects 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

Wright 1976a (*Continued*)

	visit. Wright 1976 1 was conducted on preschool children, subjects from one classroom received all one dose of vaccine. Eight children from another classroom consisting of 12 subjects received vaccine, whereas the remaining 4 was given saline solution in double-blind manner. Three of these 4 control received one dose of vaccine 6 weeks later. Study subjects 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 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.
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

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

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 within3 months before vaccination, administration of nasal medication during the first 10 days after vaccination, no telephone in the household. Five hundred were enrolled.
Interventions	"Subject were randomised into five groups to receive one 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).

Zangwill 2001 (*Continued*)

	Group 5: placebo of egg allantoic fluid containing sucrose-phosphate glutamate. Each preparation was as intranasal spray administered in two doses of 0,5 ml (0,25 ml per nostril) about 60 days apart. Five hundred 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, subjects 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.
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

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

h = hours
yrs = years
ARIs = acute respiratory tract infections
AOM - acute otitis media
URTI - upper respiratory tract infection

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

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
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

(*Continued*)

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 79
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
El'shina 1998	Age group 18 to 23
Feldman 1985	Only serological outcomes presented
Foy 1981	No control
France 2004	Case cross-over
Gaglani 2004	Ecological study
Gendon 2004a	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

(*Continued*)

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
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
Hoskins 1979	No control
Howell 1964a	Adult population
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 17.9); efficacy outcomes only serological
Hurwitz 2000a	Hepatitis A vaccine as control
Hurwitz 2000b	Hepatitis A vaccine as control
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)
Kramarz 2001	Study subjects are children with asthma

(*Continued*)

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
Martin Moreno 1998	Review
Maynard 1968	No placebo control
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
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 not split by three study years
Piedra 2002b	All the data in this paper is presented in either Piedra 2002 and King 1998, both included

(*Continued*)

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
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
Zhilova 1986	Study population aged 18 to 23

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	5	6001	Risk Ratio (M-H, Random, 95% CI)	0.18 [0.11, 0.29]
1.1 under 2 years	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.2 under 6 years	5	5941	Risk Ratio (M-H, Random, 95% CI)	0.15 [0.10, 0.23]
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)	Not estimable
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)	Not estimable
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)	Not estimable
1.2 under 6 years	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
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)	Not estimable
2.2 under 6 years	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.3 over 6 years	2	22077	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.57, 0.69]

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	10	11762	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.42, 0.70]
2.1 under 2 years	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.2 under 6 years	4	6896	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.65, 1.01]
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	5	4962	Risk Ratio (M-H, Random, 95% CI)	0.19 [0.10, 0.39]
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]
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]

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)	Not estimable
2 Influenza-like illness	4	19044	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.65, 0.79]
2.1 Inactivated vacines (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 Physician consulations for influenza	1	37	Odds Ratio (M-H, Fixed, 95% CI)	0.87 [0.12, 6.46]
1.1 Children aged below 5, with no time restriction	1	10	Odds Ratio (M-H, Fixed, 95% CI)	3.00 [0.12, 73.64]
1.2 Children aged below 5-19, with no time restriction	1	27	Odds Ratio (M-H, Fixed, 95% CI)	0.37 [0.02, 8.07]
2 Influenza-like illness	1	488	Odds Ratio (M-H, Random, 95% CI)	0.49 [0.28, 0.86]
2.1 Inactivated vaccine - one dose	1	244	Odds Ratio (M-H, Random, 95% CI)	0.53 [0.26, 1.07]
2.2 Inactivated vaccine - two doses	1	244	Odds Ratio (M-H, Random, 95% CI)	0.44 [0.18, 1.10]

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)	Not estimable
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 vacines (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)	Not estimable
3.2 Live attenuated vaccines (two doses)	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
3.3 Inactivated vacines (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)	Not estimable
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)	Not estimable
4.3 Inactivated vacines (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)	Not estimable
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)	Not estimable
5.3 Inactivated vacines (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)	Not estimable
6 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 vacines (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 otitis media	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 Inactivated vaccine, 2 doses	2	765	Risk Ratio (M-H, Random, 95% CI)	1.41 [0.62, 3.24]

8 Consequences of otitis media	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
8.1 Inactivated vaccine, 2 doses - visits	2	765	Mean Difference (IV, Random, 95% CI)	-0.02 [-0.27, 0.23]
8.2 Inactivated vaccine, 2 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 (1 dose)	1	1090	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.49, 0.85]
9.2 Live attenuated vaccine (2 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]

Comparison 9. Vaccine versus no intervention

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Influenza	1	1951	Risk Ratio (M-H, Random, 95% CI)	0.11 [0.03, 0.49]
1.1 Live attenuated vaccines (one dose)	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.2 Live attenuated vaccines (two doses)	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.3 Inactivated vaccines (one dose)	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.4 Inactivated vaccines (two doses)	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.5 Virosomal vaccine	1	1951	Risk Ratio (M-H, Random, 95% CI)	0.11 [0.03, 0.49]
2 Influenza-like illness	4	91184	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.42, 0.63]
2.1 Live attenuated vaccines (one dose)	1	21909	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.57, 0.69]
2.2 Live attenuated vaccines (two doses)	1	66980	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.63, 0.67]
2.3 Inactivated vacines (one dose)	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.4 Inactivated vaccines (two doses)	1	344	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.21, 0.51]
2.5 Virosomal vaccine	1	1951	Risk Ratio (M-H, Random, 95% CI)	0.26 [0.17, 0.40]
3 Secondary cases	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
3.1 Live attenuated vaccines (one dose)	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable

3.2 Live attenuated vaccines (two doses)	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
3.3 Inactivated vacines (one dose)	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
3.4 Inactivated vaccines (two doses)	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
4 School absenteeism (longer then 4 days)	1	344	Risk Ratio (M-H, Random, 95% CI)	0.14 [0.07, 0.27]
4.1 Live attenuated vaccines (one dose)	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
4.2 Live attenuated vaccines (two doses)	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
4.3 Inactivated vacines (one dose)	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
4.4 Inactivated vaccines (two doses)	1	344	Risk Ratio (M-H, Random, 95% CI)	0.14 [0.07, 0.27]
5 Lower respiratory tract disease	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
5.1 Live attenuated vaccines (one dose)	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
5.2 Live attenuated vaccines (two doses)	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
5.3 Inactivated vacines (one dose)	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
5.4 Inactivated vaccines (two doses)	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
6 Otitis media	1	344	Risk Ratio (M-H, Random, 95% CI)	0.13 [0.01, 2.59]
6.1 Live attenuated vaccines (one dose)	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
6.2 Live attenuated vaccines (two doses)	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
6.3 Inactivated vaccines (one dose)	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
6.4 Inactivated vaccines (two doses)	1	344	Risk Ratio (M-H, Random, 95% CI)	0.13 [0.01, 2.59]
7 Socioeconomic impact	1	909	Mean Difference (IV, Random, 95% CI)	-0.90 [-1.99, 0.19]
7.1 Inactivated vaccine - febrile respiratory illness	1	303	Mean Difference (IV, Random, 95% CI)	-0.85 [-1.42, -0.28]
7.2 Inactivated vaccine - hospital stays	1	303	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.07, 0.05]
7.3 Inactivated vaccine - school days missed	1	303	Mean Difference (IV, Random, 95% CI)	-4.23 [-6.81, -1.65]
8 Antibiotic consumption	1	1951	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.66, 0.98]
8.1 Virosomal vaccine	1	1951	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.66, 0.98]
9 School absenteism (all episodes)	1	1951	Odds Ratio (M-H, Random, 95% CI)	0.42 [0.34, 0.51]
10 Work absenteism (all episodes)	1	1951	Odds Ratio (M-H, Random, 95% CI)	0.69 [0.51, 0.93]

WHAT'S NEW

Last assessed as up-to-date: 29 September 2007.

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 retrospective 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).
15 January 2008	Amended	Converted to new review format.
10 November 2007	New citation required and conclusions have changed	Substantive amendment

HISTORY

Protocol first published: Issue 3, 2004

Review first published: Issue 1, 2006

CONTRIBUTIONS OF AUTHORS

Tom Jefferson (TOJ) - wrote background and methods; data interpretation; wrote results and discussion (efficacy and effectiveness).

Alessandro Rivetti (AR) - conducted searches; co-ordinated retrieval of papers; determined papers for inclusion; data extraction, data checking.

Anthony Harnden (AH) - conception of idea for review; formed working group and preliminary work; appointed and supervised primary author; critical review and amendments of results and conclusions.

Carlo Di Pietrantonj (CDP) - constructions of comparisons for meta analysis, data checking, data analysis, data interpretation, wrote statistical methods.

Vittorio Demichelli (VD) - wrote background and methods, determined papers for inclusion, arbitration of quality assessment; construction of comparisons for meta-analysis; critical review.

For the 2007 update AR carried out the searches and co-extracted the data with TOJ. CDP carried out statistical analyses and all authors contributed to the revised text.

DECLARATIONS OF INTEREST

None known.

APPENDIX 1 - Included studies design

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 Trail (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 Semi-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 - 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) *

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

APPENDIX 3 - 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)

Sub-group 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

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)

SOURCES OF SUPPORT

Internal sources

- REGIONE PIEMONTE ASL 20 ALESSANDRIA, Italy.
- MRC Programme Grant G0000340, UK.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Adolescent; Influenza, Human [*prevention & control]; Influenza Vaccines [*therapeutic use]; Randomized Controlled Trials as Topic; Vaccines, Attenuated [therapeutic use]; Vaccines, Inactivated [therapeutic use]

MeSH check words

Child; Child, Preschool; Humans; Infant