Assessment of the efficacy and effectiveness of influenza vaccines in healthy children: systematic review

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See Comment

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Summary

Background **We aimed to assess evidence of efficacy and effectiveness of live attenuated and inactivated influenza vaccines in children up to 16 years of age.**

Methods **We searched the Cochrane Library, MEDLINE, EMBASE Biological Abstracts, and Science Citation Index to June, 2004, in any language, and contacted vaccine manufacturers and authors of relevant studies to identify additional data. We included randomised, cohort, and case-control studies comparing efficacy of vaccines against influenza (reduction in laboratory-confirmed cases), effectiveness of vaccines against influenza-like illness (reduction in symptomatic cases), or both, with placebo or no intervention. We analysed the following outcomes: influenza, influenza-like illness, admissions, school absences, complications, and secondary transmission.**

Findings **We included 14 randomised controlled trials, eight cohort studies, one case-control study, and one randomised controlled trial of intraepidemic use of the vaccines. Live attenuated influenza vaccines had 79% efficacy and 38% effectiveness in children older than 2 years compared with placebo or no immunisation. Inactivated vaccines had lower efficacy (65%) than live attenuated vaccines, and in children aged 2 years or younger they had similar effects to placebo. Effectiveness of inactivated vaccines was about 28% in children older than 2 years. Vaccines were effective in reducing long school absences (relative risk 0·14 [95% CI 0·07–0·27]). Studies assessing the effects of vaccines against secondary cases, lower-respiratory tract disease, acute otitis media, and hospital stay suggested no difference with placebo or standard care, but lacked statistical power.**

Interpretation **Influenza vaccines (especially two-dose live attenuated vaccines) are efficacious in children older than 2 years. Efficacy and effectiveness of the vaccines differed strikingly. Only two small studies assessed the effects of influenza vaccines on hospital admissions and no studies assessed reductions in mortality, serious complications, and community transmission of influenza. If influenza immunisation in children is to be recommended as public-health policy, large-scale studies assessing such important outcomes and undertaking direct comparisons of vaccines are urgently needed.**

Introduction

Efforts to prevent the yearly spread of influenza have centred on the use of vaccines. Up to now, immunisation campaigns and coverage have targeted people age 65 years or older. In a non-pandemic situation, the choice of preventive strategy lies in immunisation of selected population categories—ie, children, elderly people, individuals with chronic pathologies, health-care workers—or the whole population. The American Academy of Paediatrics and the US Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices[1] have recommended that influenza immunisation of children age 6–23 months should be instituted as a public-health measure beginning in the 2004–05 influenza season. A statement from May, 2004, by the Advisory Committee on Immunization Practices entitled *Prevention and Control of Influenza*[2] also recommends that people in close contact with children age 0–23 months should be immunised. In Canada, the National Advisory Committee on Immunization[3] followed suit in February, 2004. The main arguments for extension of immunisation to healthy children age 6–23 months[4–6] and those attending school[6,7] include reduction of: the number of patients with influenza; the number of excess admissions; mortality of elderly people in families with children; health-care contacts (eg, family doctors); the number of antibiotic prescriptions; and absenteeism for both children and household contacts.

Rational decision-making about prevention of influenza is complicated by the absence of reliable forecasts of the effect of the virus and by uncertainties about the effects of the vaccines in different age-groups. In a Cochrane review of influenza vaccines in healthy adults,[8] a striking difference was noted between the efficacy against influenza (reduction in laboratory confirmed cases) and effectiveness against influenza-like illness (reduction in symptomatic cases) of the vaccines. Accurate assessment of the efficacy and effectiveness of influenza vaccines is essential to allow reasoned choice between alternative strategies. We aimed to identify and assess comparative studies evaluating the efficacy and effectiveness of influenza vaccines in healthy children age 16 years or younger. Our review is part of a forthcoming larger Cochrane review including evidence of safety of the vaccines.[9]

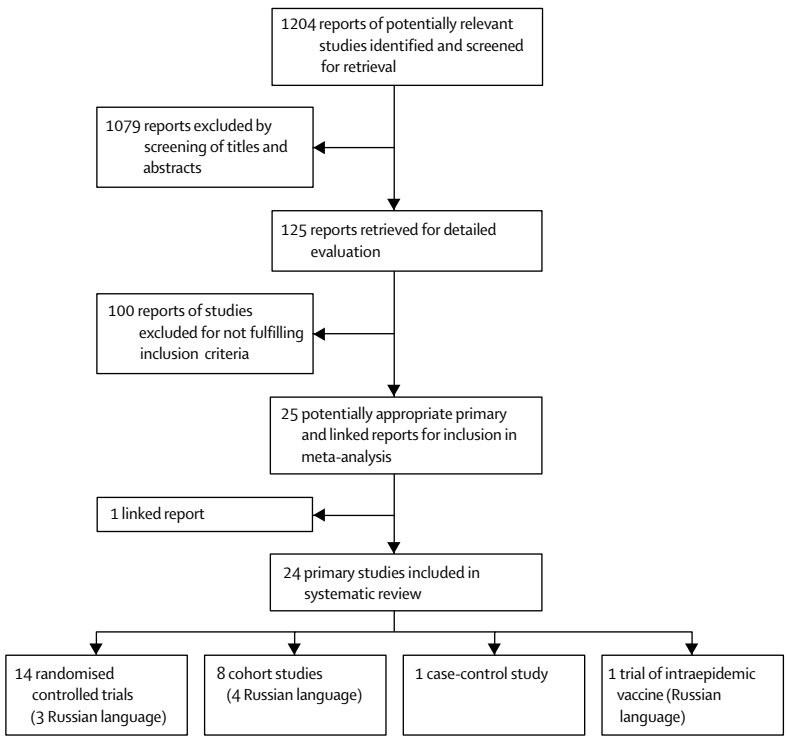

Figure 1: **Flow of studies into the review**

Methods

Searches

To identify reports of studies and systematic reviews, we searched the following electronic databases to the end of May, 2004: the Cochrane Library, including the Cochrane Database of Systematic Reviews, the NHS Database of Abstracts of Reviews of Effectiveness, and the Cochrane Central Register of Controlled Trials (CENTRAL); MEDLINE (OVID, from January, 1966); EMBASE (Dialog', 1974–79; SilverPlatter, from 1980); Biological Abstracts (SilverPlatter, from 1969); and Science Citation Index (Web of Science, from 1974). We undertook searches in any language. A detailed search strategy is available in webappendix 1 (http://image.thelancet.com/extras/04art9306webappendix1.pdf).

To identify additional published and unpublished studies, we searched the Science Citation Index to identify articles that cite relevant studies. We also keyed these studies into PubMed and used the Related Articles feature. We assessed bibliographies of all relevant articles obtained and any published reviews for additional studies. If we needed clarification on reporting we contacted vaccine manufacturers or first or corresponding authors of studies.

Selection

We selected randomised clinical trials, cohort studies, and case-control studies (webappendix 2; http://image.thelancet.com/extras/04art9306webappendix2.pdf) assessing immunisation of children age 16 years or younger in any geographical location with any influenza vaccine given independently, in any dose, preparation, or time schedule, compared with placebo or with no intervention. We decided to include evidence from comparative non-randomised studies to enhance the relevance of the review.

We considered the following primary outcome measures when selecting studies: preventive efficacy and effectiveness; cases of influenza confirmed by viral isolation, serological support, any other type of laboratory testing for viral identification (influenza cases), or a combination of these; cases of influenza-like illness within 1 year of immunisation; admissions for influenza-like illness or influenza; deaths (due to influenza-like illness or influenza); and any other direct or indirect indicator of disease impact. We did not consider serological outcome data because our aim was to assess evidence of the public-health impact of immunisation.

Data extraction and study validity assessment

Two of us (SS and AR) independently applied inclusion criteria to all identified and retrieved articles and then extracted data from included studies on standard Cochrane Vaccines Field forms. The procedure was supervised and arbitrated by TJ and VD.

We assessed methodological quality for randomised controlled trials with criteria from the Cochrane reviewers' handbook.[10] We evaluated studies according to randomisation, generation of the allocation sequence, allocation concealment, blinding, and follow-up. We assessed quality of non-randomised studies in relation to the presence of potential confounders. We used Newcastle-Ottawa scales to evaluate studies.[11] Because of the scarcity of empirical evidence for the effect that methodological quality has on the results of non-randomised studies, we used quality at the analysis stage as a means of interpretation of the results by undertaking a stepwise sensitivity analysis. Full details of quality assessment are available from the corresponding author.

We entered extracted data into Cochrane RevMan software (version 4.2; Cochrane Collaboration, Oxford, UK). Aggregation of data was dependent on the sensitivity and homogeneity of definitions of exposure, populations, and outcomes used. When studies were homogenous, we did a meta-analysis within each design category. We summarised efficacy and effectiveness estimates as relative risk with 95% CIs. Absolute vaccine efficacy was calculated as 1 minus the relative risk and expressed as a percentage.

We undertook a stepwise sensitivity analysis by excluding studies done in the former USSR from our meta-analysis. We also did a subgroup analysis when data were available for type of vaccine administered, age

of individuals, and specificity of outcome definitions. Age stratification (⩽2 years, ⩽6 years, and >6 years) indicates the most common stratification reported in included studies. To assess the effect on statistical heterogeneity, we calculated I^2 for every pooled estimate.[12] This statistic can be interpreted as the proportion of total variation among effect estimates that is attributable to heterogeneity rather than sampling error, and it is intrinsically independent of the number of studies. When I^2 is less than 30% there is little concern about statistical heterogeneity.[12–14] We used random-effect models to account for the between-study variance in our findings.[15]

Role of the funding source

The sponsor had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

From the 1204 titles identified by our searches, we selected and retrieved 125 reports of studies possibly fulfilling inclusion criteria (figure 1). 100 reports were excluded. The most frequent reason for exclusion was lack of independent controls (n=29) and non-comparative design (n=15). A complete list with reasons for exclusion is available on request from the corresponding author.

Table 1 provides a synopsis of included studies. Of the 25 included reports, 14 were of randomised controlled trials;[16–29] we also identified one randomised trial on intraepidemic use of live, orally administered vaccine.[30] Nine reports were of eight cohort studies:[31–39] one report[32] was a reanalysis of a previous study[31] with further data, and thus we deemed the publications two reports of the same study. One report was of a case-control study.[40] Three of the randomised trials[22,29,30] and five reports of cohort studies[31–34,39] were translated from Russian. Two of these studies[31–33] were classified as cohort studies because randomisation had not been mentioned in the text.

In six randomised placebo-controlled trials, influenza was reported as an outcome measure (combined denominator 5052).[17–20,23,24] Other outcomes were influenza-like illness in four reports (93 023),[16,20,23,28] symptoms of upper-respiratory infection in four (29 498),[20,22,23,28] secondary cases (infected by contacts) in one (123),[23] absences from school in one (550),[25] lower-respiratory tract disease in two (1550),[18,20] acute otitis media in three (2298),[18,20,24] and consequences of acute otitis media in one (765).[24] None of the three randomised controlled trials with a no-intervention group had influenza as an outcome measure. Influenza-like illness was an outcome in two reports (combined denominator 67 324),[21,29] absences from school for more than 4 days and acute otitis media were outcomes in one study (344),[21] and socioeconomic impact (febrile respiratory illness, number of days in hospital, and school days missed) was the outcome in another report (303).[26] Influenza was an outcome measure for four cohort studies (combined denominator 1912)[33,36–38] and influenza-like illness was one for six studies (8593).[31–36,39]

In the validity assessment, two trials scored highly for all criteria.[17,24] Nine trials had adequate randomisation[17–19,21,24–26,28,30] and in the remaining six, randomisation was inadequate or unclear. Allocation was concealed adequately in six of the placebo-controlled trials.[16,17,19,23,24,27] Eight trials documented losses to follow-up[17,19,20,23–25,28,30] and sufficient data were provided in these reports to enable us to undertake intention-to-treat analysis. Two cohort studies scored highly on all items.[33,37] The case-control study was adequately undertaken and reported but no odds ratios were provided.[40]

We did five main comparisons in our meta-analysis: three included evidence from randomised controlled trials (comparisons 1–3) and two had data from cohort studies (comparisons 4 and 5). Comparisons 1 and 4 included findings for live attenuated vaccines whereas comparisons 2 and 5 used data for inactivated vaccines. All comparators were placebo or no intervention and comparisons 1, 2, 4, and 5 were stratified by available age-groups (⩽2 years, ⩽6 years, and >6 years) and type of outcome (influenza, comparisons 1, 2, 4, 5; influenza-like illness, comparisons 1a, 2a, 4a, 5a). Comparison 3 included data for impact outcomes (secondary cases, school absences, lower-respiratory tract disease, acute

	Study design	Vaccine type	Control
Alexandrova 1986[16]	RCT	Live	Placebo
Belshe 1998[17]	RCT	Live	Placebo
Belshe 2000[18]	RCT	Live	Placebo
Beutner 1979[19]	RCT	Live and inactivated	Placebo
Clover 1991[20]	RCT	Live and inactivated	Placebo
Colombo 2001[21]	RCT	Inactivated	No intervention
Grigor'eva 2002*[22]	RCT	Live	Placebo
Gruber 1990[23]	RCT	Live and inactivated	Placebo
Hoberman 2003[24]	RCT	Inactivated	Placebo
Khan 1996[25]	RCT	Live and inactivated	Placebo
Principi 2003[26]	RCT	Inactivated	No intervention
Rudenko 1993[27]	RCT	Live and inactivated	Placebo
Rudenko 1996[28]	RCT	Live	Placebo
Rudenko 1996*[29]	RCT	Live	No intervention
Slepushkin 1974*[30]	RCT (intraepidemic)	Live	Unclear
Bashliaeva 1986*†[31] and Chumakov 1987*†[32]	Cohort study	Inactivated	Placebo
Burtseva 1991*†[33]	Cohort study	Live and inactivated	Placebo
El'shina 2000*[34]	Cohort study	Inactivated	No intervention
Jianping 1999[35]	Cohort study	Inactivated	No intervention
Kawai 2003[36]	Cohort study	Inactivated	No intervention
Maeda 2002[37]	Cohort study	Inactivated	No intervention
Maeda 2004[38]	Cohort study	Inactivated	No intervention
Slobodniuk 2002*[39]	Cohort study	Inactivated	No intervention
Hirota 1992[40]	Case-control	Inactivated	

RCT=randomised controlled trial. *Translated from Russian. †Classified as cohort study because randomisation not referred to in text.

Table 1: **Included studies**

otitis media and its consequences, and hospital stay). Because of scarcity of data (most outcomes were reported by one or two studies only), no age or stratification was possible for comparison 3.

Figure 2 outlines the assessment of vaccine efficacy. In comparison 1, live attenuated vaccines had 79% overall efficacy, although no usable data were recorded in children age 2 years or younger. In one study of 1602 children age 15–71 months, estimates of vaccine efficacy were reported in the discussion section of 86% (95% CI 65–94) in 1-year-olds and 96% (86–99) in 2-year-olds.[17] Without an age breakdown these data cannot be included in the meta-analysis. Comparison 2 showed that inactivated vaccines had an efficacy of 65%, which is a lower value than that for live attenuated vaccines, although the difference is not significant. In children aged 2 years or younger, inactivated vaccines were no more efficacious than placebo (24%), although this observation was based on one small study.[24] In comparison 4, live attenuated vaccines were 44%

	Vaccine (n/N)	Placebo (n/N)	Weight (%)	Relative risk (random) 95% CI	I^2 (%)
Comparison 1					
Age 2 years or younger (0 studies)	No data available				
Age 6 years or younger (3 studies)	34/2014	166/1024	75·50	0·16 (0·06–0·42)	84·6
Older than 6 years (1 study)	7/29	16/31	24·50	0·47 (0·23–0·97)	0
Total	41/2043	182/1055	100·00	0·21 (0·08–0·52)	86·9
Comparison 1a					
Age 2 years or younger (0 studies)	No data available				
Age 6 years or younger (5 studies)	4706/18 841	6787/17 734	37·59	0·58 (0·49–0·68)	92·1
Older than 6 years (7 studies)	10 483/69 909	17 561/74 476	62·41	0·63 (0·57–0·70)	92·0
Total	15 189/88 750	24 348/92 210	100·00	0·62 (0·57–0·67)	91·2
Comparison 2					
Age 2 years or younger (2 studies)	24/525	24/261	21·97	0·76 (0·12–4·71)	80·1
Age 6 years or younger (2 studies)	12/54	39/78	24·98	0·42 (0·14–1·20)	65·7
Older than 6 years (4 studies)	44/574	164/541	53·05	0·28 (0·20–0·40)	10·6
Total	80/1153	227/880	100·00	0·35 (0·24–0·53)	52·5
Comparison 2a					
Age 2 years or younger (0 studies)	No data available				
Age 6 years or younger (2 studies)	5/54	14/78	0·57	0·52 (0·14–1·98)	33·0
Older than 6 years (4 studies)	1776/8432	3115/10 480	99·43	0·72 (0·66–0·78)	34·1
Total	1781/8486	3130/10 558	100·00	0·72 (0·67–0·78)	18·6
Comparison 4					
Age 2 years or younger (0 studies)	No data available				
Age 6 years or younger (0 studies)	No data available				
Older than 6 years (1 study)	14/39	28/44	100·00	0·56 (0·33–0·91)	0
Comparison 4a					
Age 2 years or younger (0 studies)	No data available				
Age 6 years or younger (0 studies)	No data available				
Older than 6 years (1 study)	15/79	27/89	100·00	0·63 (0·36–1·09)	0
Comparison 5					
Age 2 years or younger (3 studies)	8/157	14/157	29·78	0·63 (0·27–1·47)	0
Age 6 years or younger (1 study)	5/86	16/94	17·28	0·34 (0·13–0·89)	NA
Older than 6 years (2 studies)	27/1032	49/347	52·94	0·36 (0·12–1·11)	86·6
Total	40/1275	79/598	100	0·42 (0·25–0·73)	49·9
Comparison 5a					
Age 2 years or younger (0 studies)	No data available				
Age 6 years or younger (3 studies)	1482/2629	821/1354	31·10	0·41 (0·12–1·42)	88·4
Older than 6 years (6 studies)	186/1794	711/2737	68·90	0·42 (0·25–0·70)	76·8
Total	1668/4423	1532/4091	100	0·43 (0·27–0·68)	93·6

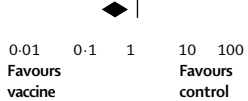

Figure 2: **Live attenuated and inactivated influenza vaccines compared with placebo or no intervention by age and study design**
NA=not applicable.

efficacious, although this observation was again based on findings of one small study.[33] Comparison 5 showed that inactivated vaccines had an efficacy of 64% in children older than 6 years, 66% in those age 6 years or younger, and were no better than placebo (37%) in children age 2 years or younger.

Figure 2 also outlines the assessment of vaccine effectiveness. In comparison 1a, live attenuated vaccines had 38% overall effectiveness, but we could find no evidence in children aged 2 years or younger. Comparison 2a showed that inactivated vaccines had 28% overall effectiveness; again, we could find no evidence in children aged 2 years or younger. In comparison 4a, live attenuated vaccines were not effective in children older than 6 years, although this observation was based on one study.[33] We could find no evidence for this comparison in the other age-groups. Comparison 5a showed that inactivated vaccines had overall 57% effectiveness, but yet again we could find no data in children age 2 years or younger. These vaccines are not effective in children age 6 years or younger, but in those older than 6 years, they were 58% effective.

The case-control study tested the effectiveness against influenza-like illness of an inactivated vaccine during an outbreak in 803 children aged 6–12 years.[40] The vaccine was well matched antigenically to the circulating strain, and its administration was inversely associated with risk of severe but not mild influenza-like illness.

Figure 3 outlines the assessment of evidence from randomised controlled trials of vaccine effectiveness on impact outcomes. Vaccines were significantly more effective than placebo or no intervention in reduction of school absence, but both these observations were based on one study.[21,25] In a third trial,[26] a significant fall in school days missed by immunised children compared with those not treated was recorded. The effects of vaccines on all other outcomes (secondary cases, lower-respiratory tract disease, acute otitis media and its consequences, and hospital stay) did not differ significantly from those of placebo or no intervention (figure 3).

Comparisons between the efficacy of one-dose and two-dose schedules of live attenuated vaccines versus placebo favoured the two-dose schedule (effectiveness 73%[17,18,20,23] *vs* 93%[17]), although the estimate for the two-dose schedule is based on one study only. In all inactivated vaccine trials a one-dose schedule was used.[19,20,23,24] Pooling data for all age-groups made no difference to our conclusions.

Table 2 shows the results of the stepwise sensitivity analysis. All comparisons, except for comparisons 1 and 2, were sensitive to the exclusion of evidence from

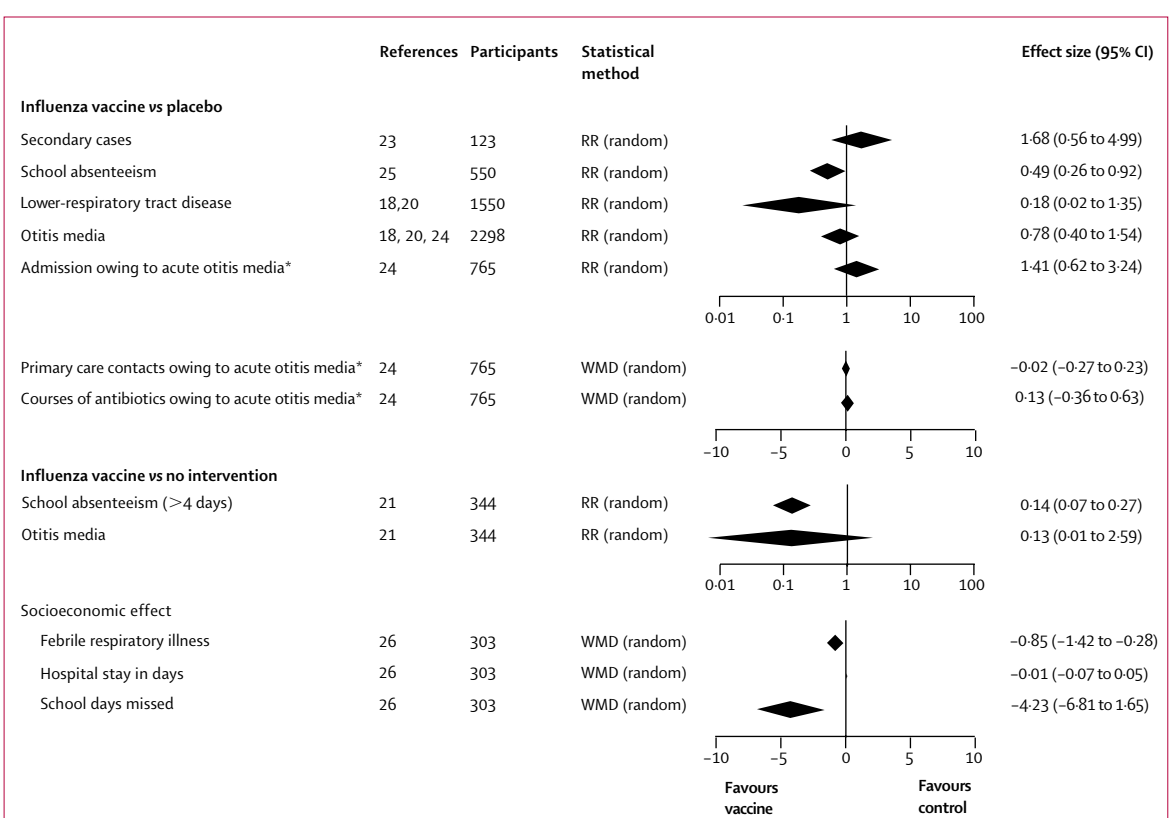

Figure 3: **Influenza vaccines versus placebo or no intervention**
RR (random)= relative risk (random effects model). WMD (random)=weight mean difference (random effects model). *Inactivated vaccine, two doses.

	Relative risk (random) [95% CI] without Russian studies	Number of independent datasets	Relative risk (random) [95% CI] for all studies	Number of independent datasets
Comparison 1—live vaccine *vs* placebo or no intervention (by age-groups) for influenza (evidence from RCTs)				
Age 2 years or younger	..	..	..	..
Age 6 years or younger	0·16 (0·06–0·42)	3	0·16 (0·06–0·42)	3
Older than 6 years	0·47 (0·23–0·97)	1	0·47 (0·23–0·97)	1
Total	0·21 (0·08–0·52)	4	0·21 (0·08–0·52)	4
Comparison 1a—live vaccine *vs* placebo or no intervention (by age-groups) for influenza-like illness (evidence from RCTs)				
Age 2 years or younger	..	..	..	..
Age 6 years or younger	0·34 (0·23–0·52)	2	0·58 (0·49–0·68)	5
Older than 6 years	0·12 (0·01 – 2·11)*	1	0·63 (0·57–0·70)	7
Total	0·33 (0·22–0·51)†	3	0·62 (0·57–0·67)	12
Comparison 2—inactivated vaccine *vs* placebo or no intervention (by age-groups) for influenza (evidence from RCTs)				
Age 2 years or younger	0·76 (0·12–4·71)	2	0·76 (0·12–4·71)	2
Age 6 years or younger	0·42 (0·14–1·20)	2	0·42 (0·14–1·20)	2
Older than 6 years	0·28 (0·20–0·40)	4	0·28 (0·20–0·40)	4
Total	0·35 (0·24–0·53)	8	0·35 (0·24–0·53)	8
Comparison 2a—inactivated vaccine *vs* placebo or no intervention (by age-groups) for influenza-like illness (evidence from RCTs)				
Age 2 years or younger	..	..	..	..
Age 6 years or younger	0·52 (0·14–1·98)	2	0·52 (0·14–1·98)	2
Older than 6 years	0·24 (0·08–0·70)†	2	0·72 (0·66–0·78)	4
Total	0·38 (0·19–0·80)†	4	0·72 (0·67–0·78)†	6
Comparison 4—live attenuated vaccine *vs* placebo (by age-groups) for influenza (evidence from cohort studies)				
Age 2 years or younger	..	..	..	..
Age 6 years or younger	..	..	..	..
Older than 6 years	No studies	..	0·56 (0·33–0·91)	1
Comparison 4a–live attenuated vaccine *vs* placebo (by age-groups) for influenza-like illness (evidence from cohort studies)				
Age 2 years or younger	..	..	..	..
Age 6 years or younger	..	..	..	..
Older than 6 years	No studies	..	0·63 (0·36–1·09)	1
Comparison 5—inactivated vaccine *vs* placebo or no intervention (by age-groups) for influenza (evidence from cohort studies)				
Age 2 years or younger	0·63 (0·27–1·47)	3	0·63 (0·27–1·47)	3
Age 6 years or younger	0·34(0·13–0·89)	1	0·34(0·13–0·89)	1
Older than 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
Comparison 5a—inactivated vaccine *vs* placebo or no intervention (by age-groups) for influenza-like illness (evidence from cohort studies)				
Age 2 years or younger				
Age 6 years or younger	0·24 (0·12–0·47)†	1	0·41 (0·12–1·42)	3
Older than 6 years	0·10 (0·05–0·21)†	1	0·42 (0·25–0·70)	6
Total	0·16 (0·08–0·31)†	2	0·43 (0·27–0·68)	9

*Significance change. †Possible decision-making significance change.

Table 2: **Sensitivity analysis**

studies done in the former USSR. In comparison 1a, exclusion of six independent datasets made the effectiveness estimate non-significant in children older than 6 years but enhanced the total effectiveness from 38% to 67%. In comparison 2a, effectiveness estimates for children older than 6 years were not significantly affected but were increased from 28% to 76%. Comparisons 4 and 4a were depopulated by the removal of the one dataset in each stratum. In comparison 5, the non-significant 64% estimate for children older than 6 years became significant (80%), whereas in comparison 5a, the estimates for those older than 6 years (58%) remained significant but increased in size (90%).

Discussion

We have shown that live attenuated influenza vaccines have good efficacy but low effectiveness in children older than 2 years. These vaccines might be effective in controlling a school outbreak; however, they are not licensed for use in children younger than 2 years. Inactivated vaccines had lower efficacy than live attenuated vaccines, and in children age 2 years or younger they had similar effects to placebo. Their effectiveness was low in children older than 2 years; we could find no evidence in those age 2 years or younger. Our conclusions about inactivated vaccines are based on more than 18 000 observations from randomised studies. Findings of cohort studies (5910 observations) suggested that inactivated vaccines had high efficacy and effectiveness in children older than 6 years, but in those younger than 2 years, efficacy was no better than that of placebo and no evidence was found of their effectiveness. Differences between efficacy and effectiveness of vaccines are not surprising because influenza vaccines are specifically targeted at influenza viruses and are not designed to prevent other causes of influenza-like illness.

We found little evidence for other outcomes. Vaccines were somewhat effective at reducing school absence, but they had little effect on other outcomes (secondary cases, lower-respiratory tract disease, acute otitis media and its

consequences, and hospital stay) compared with placebo or no intervention. However, these conclusions are based on few studies.

Studies from Russia have rarely been included in discussion of this topic. Our report included seven studies translated from Russian. Exclusion of these studies from the former USSR did not materially affect our conclusions but made our estimates more unstable. We have no reason to believe that vaccines produced in the former USSR have different performance from their western counterparts. The only placebo-controlled study directly comparing the effectiveness of trivalent inactivated split-virus vaccine with trivalent live attenuated, cold-adapted influenza vaccine on school absences failed to show any difference in performance.[25]

Our review has several potential limitations. First, we could not find sufficient data to allow us to draw firm conclusions on immunisation routes (intramuscular or intranasal) or one-dose or two-dose schedules in inactivated vaccines. Second, our meta-analysis found significant heterogeneity, which could be attributable to several factors. For example, differences in between-study follow-up periods (the longer the follow-up the more the potential for identification of cases with vaccine dilution as viral circulation declines), influenza-like illness case definitions (our sensitivity analysis failed to show differences in case definition specificity), performance of live vaccines, case-finding and study quality, and circulating viral concentrations could have caused heterogeneity. Finally, included studies provided insufficient data to stratify for viral circulation or duration of follow-up, but we do not believe heterogeneity affected our conclusions because our estimates are unequivocal and all point to high efficacy and low effectiveness of the vaccines.

The general methodological quality of included studies was reasonable, although we noted that description of vaccine content was variable and no preservatives or excipients were reported. We could find few comments 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.[8] 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.

In conclusion, we have identified a large dataset showing reasonable quality evidence of efficacy of influenza vaccines in children age 2 years or older, especially for two-dose live attenuated vaccines. However, we noted a striking difference between efficacy and effectiveness of vaccines because of the large proportion of influenza-like illness caused by agents other than influenza viruses, a finding that accords with a Cochrane review of influenza vaccines in healthy adults.[8] This point is important in the decision to immunise whole populations. Immunisation of very young children is not lent support by our findings. Although a growing body of evidence shows the effect of influenza on admissions and deaths of children, we recorded no convincing evidence that vaccines can reduce mortality, admissions, serious complications, and community transmission of influenza.

Contributors

T Jefferson, V Demicheli, and A Harnden designed and supervised the conduct of the study. S Smith and V Demicheli wrote the protocol. A Rivetti and S Smith did the searches, applied inclusion criteria, and extracted data. T Jefferson and V Demicheli arbitrated and checked the data extraction. V Demicheli and C Di Pietrantonj did the meta-analysis and statistical testing. T Jefferson and A Harnden wrote the final report. All authors contributed to both the protocol and final report.

Conflict of interest statement

TJ has received consultancy fees from Sanofi Synthelabo and previously owned shares in GlaxoSmithKline. All other authors declare that they have no conflict of interest.

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