Seasonal influenza vaccine efficacy and its determinants in children and non-elderly adults: a systematic review with meta-analyses of controlled trials
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CRD summary
Authors concluded that influenza vaccines were efficacious for the prevention of influenza but efficacy depended on variables such as type of vaccine. Reporting of the review process was somewhat limited. The authors’ conclusions broadly reflected the large evidence base although evidence of efficacy was restricted to non-elderly populations. The authors’ recommendations for cautious interpretation of several analyses appear appropriate.

Authors’ objectives
To assess the efficacy of seasonal influenza vaccine for the prevention of influenza in children and non-elderly adults.

Searching
MEDLINE and EMBASE were searched up to October 2011 for publications in English, French, Spanish and Russian. Search terms were reported. References of relevant articles and studies presented at major medical meetings between 2009 and 2011 were searched manually.

Study selection
Eligible studies were randomised controlled trials (RCTs) or quasi-RCTs. Trials had to compare the effects of seasonal influenza vaccines versus placebo, inactive control or no intervention on incidence of laboratory-confirmed influenza in children and non-elderly adults. Eligible vaccine types were inactivated parenteral, live-attenuated intranasal, adjuvanted or recombinant. Studies that randomised or allocated participants at the group level, focused on special populations (elderly, immunosuppressed or frail individuals) or explored efficacy after experimental challenge as opposed to natural infection were excluded from the review.

Included studies were published between 1970 and 2011 and seasons ran between 1968 and 2009. Participants were healthy children or non-elderly adults from 26 countries.

The authors did not state how many reviewers screened studies for inclusion.

Assessment of study quality
Study quality was assessed according to the Jadad score. Studies that scored less than 3 were categorised as low quality, studies that scored 3 were moderate quality and studies that scored 4 or 5 were categorised as high quality.

The authors did not state how many reviewers performed the quality assessment.

Data extraction
The incidence of influenza in intervention and control groups was extracted to calculate risk ratios (RR) and 95% confidence intervals (CI).

The authors did not state how many reviewers extracted data.

Methods of synthesis
A Mantel-Haenszel random-effects model was used to pool risk ratios and 95% CI. Statistical heterogeneity was assessed using the $I^2$ statistic ($I^2>50\%$ was considered evidence of heterogeneity).

Separate analyses were conducted by type of vaccine, type of laboratory confirmed influenza, age group, overall adequacy of vaccine strain matching for the study season, incidence of influenza caused by strains matched or not matched to the vaccine (as defined in the review). Sensitivity analyses were performed in studies considered high quality only.

Publication bias was assessed using funnel plots and Egger’s test.
Results of the review

Thirty studies (88,468 participants) were included in the review. Five studies were of low quality, seven moderate quality and 18 studies were high quality.

One hundred and one analyses were performed, with 93 evaluating heterogeneity. Significant statistical heterogeneity was identified for 46 of 93 analyses (full details reported in the review).

The overall efficacy of influenza vaccine was 65% compared to controls (RR 0.35, 95% CI 0.29 to 0.43; I²=75%; 23 studies).

Efficacy of vaccines was highest against infections that matched the vaccine formulation (RR 0.22, 95% CI 0.16 to 0.30; I²=72%; 10 studies) and lowest for infections that did not match the vaccine (RR 0.45, 95% CI 0.31 to 0.65; I²=69%; nine studies). Similarly, vaccine efficacy was highest compared to controls when there was good vaccine match to the circulating seasonal strains (RR 0.32, 95% CI 0.22 to 0.46; I²=82%; 11 studies) and lowest when vaccines were poorly matched to seasonal strains (RR 0.41, 95% CI 0.28 to 0.61; I²=65%; eight studies).

There was evidence of effect modification according to vaccine type and age group, influenza type and type of case ascertainment method (results fully reported in the review).

Sensitivity analyses in only high quality studies did not statistically significantly alter the findings.

There was no evidence of publication bias.

Authors’ conclusions

Influenza vaccines were efficacious for the prevention of influenza. However, vaccine efficacy depends on several variables including type of vaccine and age of vaccinee, degree of matching between the circulating and vaccine strains, influenza type and methods used for endpoint ascertainment.

CRD commentary

The review question and supporting inclusion criteria were stated clearly. The literature search was limited to two databases and restricted by language so relevant data may have been missed. The authors reported that there was no evidence of publication bias. It was unclear how many reviewers performed each stage of the review process reviewer error and bias may have been introduced.

Large numbers of studies and participants were included in the review but few details were reported. Appropriate methods were used to assess study quality and this was taken into account in the statistical analysis. A large number of analyses showed statistical heterogeneity and appropriate methods were used to go some way to explore this. The authors acknowledged that their review did not assess adverse effects of vaccinations, that there was heterogeneity between studies and that some outcomes should only be considered as exploratory due to the wide confidence intervals reported. In addition, consideration should be given to the variability in geographical location and differences over time (the publications extended over 38 years).

Two reviewers were employees at a pharmaceutical company.

The reporting of the review process was limited but the evidence base was large and the findings were generally consistent. The authors’ conclusions broadly reflected the evidence presented but interpretation should take into account that efficacy was shown only in populations other than high risk groups such as the elderly. The authors’ recommendations for cautious interpretation of several analyses seem appropriate and caution may need to be extended to other subgroup analyses.

Implications of the review for practice and research

Practice: The authors did not state any implications for practice.

Research: The authors stated a need for further research to explore the effects of other variables such as vaccine manufacturer, use of adjuvants, race, ethnicity and geography on the efficacy of influenza vaccines.
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