Prevention of influenza in the general population
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CRD summary
This review, which evaluated the effectiveness of influenza vaccine and prophylactic neuraminidase inhibitors in the general population, concluded that there is evidence to suggest moderate effectiveness. This conclusion is weakened by the poor reporting of the review process. In addition, wide variations in efficacy suggest that other factors need consideration when interpreting the evidence.

Authors' objectives
To determine the effectiveness of influenza vaccine and prophylactic neuraminidase inhibitor antiviral agents for the prevention of influenza in healthy adults and children.

Searching
MEDLINE (1966 to 2003) and the Cochrane Library were searched for studies published in English or French; the search terms were reported.

Study selection
Study designs of evaluations included in the review
Quasi-randomised and randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Studies of influenza vaccines or prophylactic neuraminidase inhibitors were eligible for inclusion. The types of influenza vaccines evaluated in included studies were inactivated or live-attenuated; the types of neuraminidase inhibitors were oseltamivir and zanamavir. The comparators included placebo, no treatment, hepatitis A vaccine, monovalent influenza B vaccine, monovalent influenza A vaccine and the diphtheria-tetanus vaccine.

Participants included in the review
Studies of healthy adults and children were eligible for inclusion. Studies that evaluated high-risk groups were excluded. The children in the influenza vaccination studies were aged from 6 months to 19 years. Oseltamivir was evaluated in those over 12 years of age, and zanamavir in those over 5 years of age.

Outcomes assessed in the review
Studies that reported an outcome measure of clinical efficacy, determined by a clinical definition of influenza or laboratory confirmed diagnosis, were eligible for inclusion. Studies of neuraminidase inhibitors reported laboratory confirmed influenza only. Studies that reported only vaccine immunogenicity were excluded. The reported outcomes included clinical events (laboratory confirmed influenza, influenza-like illness, febrile illness and respiratory illness) and other outcomes related to economic burden (hospital admission, antibiotic use for respiratory infection, visits to a health care provider, lost work days and absenteeism from school or daycare).

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
Each included study was assigned a quality rating of 'good', 'fair' or 'poor' according to the U.S. Preventive Service Task Force. The authors did not state how many reviewers performed the quality assessment.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. Data were extracted on the rate per 100 of each outcome in the vaccination and control groups, along with the corresponding relative risk reduction (RRR) and 95% confidence interval, significance value and number-needed-to-treat.

Methods of synthesis
How were the studies combined?
The results of individual studies were tabulated and combined in a narrative format, grouped separately for influenza vaccine trials of adults and children, and for antiviral trials using neuraminidase inhibitors.

How were differences between studies investigated?
Differences between the studies were evident from the tabulated results and were discussed in the narrative with regards to type of vaccine administered.

Results of the review
Thirty-three influenza vaccine RCTs were included in the review; 18 (n more than 33,000) were performed in healthy adults and 15 (n more than 45,000) in healthy children. Six antiviral RCTs (n=3,368) were included in the review.

Influenza vaccination in healthy adults.

Eleven studies were considered to be ‘good’ quality and 7 were considered ‘fair’.

The rate of laboratory confirmed influenza ranged from 1.3 to 20 per 100 in the control group and from 0.3 to 5.3 per 100 in the vaccination group. The rates of clinical event ranged from 1.6 to 26 per 100 and from 2 to 27.9 per 100 in the control and vaccination groups, respectively.

The RRR ranged from 0 to 91%.

Thirteen studies reported adverse events. The most frequent side-effects were local site symptoms including pain, redness and irritation. Live-attenuated vaccines were significantly more likely to cause runny nose (1 study) or a sore throat (3 studies) compared with placebo.

Influenza vaccination in healthy children.

Nine studies were considered to be ‘good’ quality and 6 were ‘fair’ quality.

Twelve studies reported a benefit associated with influenza vaccination. The rate of clinical event ranged from 5.75 to 51 per 100 in the control group and from 0.88 to 36 per 100 in the vaccination group. The RRR ranged from 0 to 93%. Three studies found no benefit in influenza vaccination; these were all considered to be of ‘fair’ quality. No difference in efficacy was found between live-attenuated and inactivated vaccines, and seasonal influenza attack rates were observed.

Twelve studies reported adverse events. The studies found that inactivated and live-attenuated vaccines were well tolerated and no severe adverse events were reported. Those given live-attenuated vaccine were significantly more likely to suffer from runny nose, coryza and fever, while those given inactivated vaccine were likely to suffer induration at the injection site. Fever was more likely in younger children than in older children for both types of vaccine.

Neuraminidase inhibitor prophylaxis.

All studies were considered to be of ‘good’ quality.

The rate of laboratory confirmed influenza ranged from 4.8 to 67 per 100 in the control group and from 1.3 to 38 per 100 in the vaccination group. The RRR ranged from 32 to 84% and the reduction in risk was found to be significant in
Six studies reported adverse events. Three studies of oseltamivir found that gastrointestinal side-effects were more frequently reported. Three studies of zanamavir found no difference in the occurrence of adverse events in comparison with placebo.

**Cost information**

Of the trials of healthy adults that considered economic burden, two reported no reduction in lost time due to respiratory illness and four reported modest reductions. One study performed a cost-benefit analysis and reported reduced costs associated with work missed, reduced effectiveness at work due to illness and visits to health care providers. The associated mean break-even cost for the vaccine and its administration was US$43.07.

**Authors' conclusions**

There was good evidence to suggest that influenza vaccination (live-attenuated and inactive) is moderately effective in preventing influenza in the general healthy population. There was also good evidence that neuraminidase inhibitor prophylaxis is effective when given to contacts within 36 to 48 hours of symptom onset of the household index case.

**CRD commentary**

The review addressed a clear research question and the inclusion criteria were appropriate. Appropriate sources were used to identify relevant studies and attempts were made to minimise language bias. It was unclear whether the study selection, quality assessment and data extraction process were performed in duplicate, thus the potential for reviewer bias and error could not be determined. From the details presented on each included study, it was evident that there were differences across studies with regards to the type of vaccine and outcome measured. Collectively, this suggests that the decision to combine the studies in a narrative was appropriate. The authors attributed the wide variation in efficacy to factors such as vaccine immunogenicity and the degree of match between vaccine strain and circulating virus. On the whole, the conclusions follow from the evidence presented, although limitations in the reporting of the review process weaken the strength of this conclusion. Furthermore, the wide variations in the efficacy highlight the need to consider other factors when interpreting the results of studies of influenza vaccination.

**Implications of the review for practice and research**

Practice: The authors stated that any decision about routine immunisation will need to account for the cost and cost-effectiveness of a universal programme and the burden of disease associated with influenza in individual jurisdictions.

Research: The authors stated that new influenza vaccines need evaluation.

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