CRD summary
The authors concluded that influenza vaccination was associated with a lower risk of major adverse cardiovascular events within one year in patients at high risk of cardiovascular events. This was a generally well-conducted review but uncertainties surrounding the generally small and heterogeneous evidence base mean the reliability of the findings remains uncertain and they should be considered preliminary.

Authors’ objectives
To assess the effects of influenza vaccination on patients at high risk of cardiovascular events.

Searching
MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched up to August 2013 without language restrictions. Search terms were reported. Reference lists of eligible articles were searched. Relevant conference abstracts (from 2000 to 2013) and ClinicalTrials.gov were screened for published and unpublished data.

Study selection
Eligible studies were randomised controlled trials (RCTs) that assessed short-term efficacy and safety (duration 28 days to one year) of influenza (flu) vaccination in adults at high risk of cardiovascular disease. Eligible trials had to include at least 50 patients and could compare flu vaccination to placebo or control, or compare a more intense versus standard vaccination. The primary outcome was a composite of major adverse cardiovascular events (as defined in the review) or where this was not reported, fatal and nonfatal myocardial infarction and stroke events. Secondary outcomes were reported.

Included trials were conducted in USA, Argentina, Thailand, Europe (including one UK trial), Iran and South Africa. Trials were published between 1994 and 2013. Most trials administered intramuscular inactivated influenza vaccine. Most of the included efficacy trials were of in-patients with recent acute coronary syndrome or stable coronary artery disease. All safety trials were in outpatients; the proportion of patients with cardiac disease ranged from 13.5% to 64.5%. The mean age of patients ranged from 52 to 83 years. Influenza activity was considered sporadic, regional or widespread (as defined in the review).

Two reviewers independently screened studies for inclusion; discrepancies were resolved through consensus.

Assessment of study quality
Trial quality and risk of bias were assessed according to the Jadad scale and Cochrane risk of bias methods with criteria on randomisation, allocation concealment, blinding, outcome reporting and other sources of bias.

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

Data extraction
Two reviewers independently extracted absolute numbers of first-occurrence events within 12 months follow-up to calculate risk ratios and 95% confidence intervals. Data were extracted on an intention-to-treat (ITT) basis. Where zero events were reported, a 0.5 correction factor was added to each treatment group.

Primary authors were contacted for further information, where necessary.

Methods of synthesis
A random-effects model was used to combine risk ratios and their 95% confidence intervals. The number needed to treat (NNT) was calculated where statistically significant outcomes were reported.
Statistical heterogeneity was assessed using the $X^2$ test and $I^2$ statistic. Separate analyses were performed in seven selected subgroups (such as trial quality and duration of follow-up) and to include unpublished data. Sensitivity analyses were performed removing one trial at a time.

Publication bias was assessed through visual inspection of funnel plots.

Results of the review

Twelve RCTs (23,592 participants) were included in the review. Follow-up durations ranged from one to 12 months. The Cochrane risk of bias tool indicated that five trials were at high risk, one was uncertain risk and six were at low risk of bias (taken from table of characteristics).

Major adverse cardiovascular events (six RCTs): The five published RCTs showed that patients who received flu vaccine had statistically significantly fewer major adverse cardiovascular events compared with placebo or control within one year of follow-up (RR 0.64, 95% CI 0.48 to 0.86; NNT 58); there was no evidence of significant statistical heterogeneity ($I^2$=28%). Subgroup analyses showed that patients with recent acute coronary syndrome (compared to placebo/control) were at lower risk of major adverse cardiovascular events with flu vaccine compared to patients with stable coronary artery disease (compared to placebo/control).

Cardiovascular mortality and all-cause mortality (six RCTs): There were no statistically significant differences between patients who received flu vaccine versus placebo or control in the risk of cardiovascular or all-cause mortality. There was evidence of significant statistical heterogeneity ($I^2$=68%).

Addition of unpublished data and sensitivity analyses did not significantly alter any of the findings. Other findings were reported in the review. There was no evidence of publication bias.

Authors’ conclusions

Influenza vaccination was associated with a lower risk of major adverse cardiovascular events within one year in patients at high risk of cardiovascular events.

CRD commentary

The review question and supporting inclusion criteria were clearly stated. A satisfactory search of the literature was conducted without restrictions on language or publication status. The authors stated that funnel plots suggested that small trials of cardiovascular benefit may remain unpublished. Trial quality was assessed using appropriate criteria and approximately half of the trials were considered to be a low risk of bias. However, there were some slight discrepancies between the presented results. It was unclear whether quality was assessed in duplicate, so reviewer error and bias could not be ruled out.

The authors acknowledged that the evidence was based on a relatively small number of cardiovascular events in trials that varied in study and patient characteristics; one of the main differences was inclusion of both primary and secondary prevention populations. The authors used appropriate statistical methods to take into account the differences and went some way to explore the underlying causes. Confidence intervals were wide for some outcomes and the direction of effect was sometimes inconsistent. Subgroup analyses were conducted in small samples sizes, which the authors acknowledged.

This was a generally well-conducted review but uncertainties surrounding the generally small and heterogeneous evidence base mean the reliability of the findings remains uncertain and they should be considered preliminary.

Implications of the review for practice and research

Practice: The authors stated that the findings provided some support for current guideline recommendations for influenza vaccination of patients with acute coronary syndrome. They stated that it was imperative to address the specific underlying causes of potential cardiovascular complications that may occur in association with influenza, particularly in elderly patients.

Research: The authors stated a need for adequately powered multicentre trials to confirm the efficacy of low-cost, annual, safe, easily administered and well-tolerated influenza vaccination to reduce cardiovascular risk beyond current therapies.
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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.