

Influenza vaccines for preventing cardiovascular disease (Review)

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[Intervention Review]

Influenza vaccines for preventing cardiovascular disease

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ABSTRACT

Background

This is an update of the original review published in 2008. The risk of adverse cardiovascular outcomes is increased with influenza-like infection, and vaccination against influenza may improve cardiovascular outcomes.

Objectives

To assess the potential benefits of influenza vaccination for primary and secondary prevention of cardiovascular disease.

Search methods

We searched the following electronic databases on 18 October 2013: *The Cochrane Library* (including Cochrane Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews of Effects (DARE), Economic Evaluation Database (EED) and Health Technology Assessment database (HTA)), MEDLINE, EMBASE, Science Citation Index Expanded, Conference Proceedings Citation Index - Science and ongoing trials registers (www.controlled-trials.com/ and www.clinicaltrials.gov). We examined reference lists of relevant primary studies and systematic reviews. We performed a limited PubMed search on 20 February 2015, just before publication.

Selection criteria

Randomised controlled trials (RCTs) of influenza vaccination compared with placebo or no treatment in participants with or without cardiovascular disease, assessing cardiovascular death or non-fatal cardiovascular events.

Data collection and analysis

We used standard methodological procedures as expected by The Cochrane Collaboration. We carried out meta-analyses only for cardiovascular death, as other outcomes were reported too infrequently. We expressed effect sizes as risk ratios (RRs), and we used random-effects models.

Main results

We included eight trials of influenza vaccination compared with placebo or no vaccination, with 12,029 participants receiving at least one vaccination or control treatment. We included six new studies (n = 11,251), in addition to the two included in the previous version of the review. Four of these trials (n = 10,347) focused on prevention of influenza in the general or elderly population and reported cardiovascular outcomes among their safety analyses; four trials (n = 1682) focused on prevention of cardiovascular events in patients with established coronary heart disease. These populations were analysed separately. Follow-up continued between 42 days and one

year. Five RCTs showed deficits in at least three of the risk of bias criteria assessed. When reported (seven studies), vaccination provided adequate immunogenicity or protection against influenza. Cardiovascular mortality was reported by four secondary prevention trials and was significantly reduced by influenza vaccination overall (risk ratio (RR) 0.45, 95% confidence interval (CI) 0.26 to 0.76; P value 0.003) with no significant heterogeneity between studies, and by three trials reporting cardiovascular mortality as part of their safety analyses when the numbers of events were too small to permit conclusions. In studies of patients with coronary heart disease, composite outcomes of cardiovascular events tended to be decreased with influenza vaccination compared with placebo. Generally no significant difference was found between comparison groups regarding individual outcomes such as myocardial infarction.

Authors' conclusions

In patients with cardiovascular disease, influenza vaccination may reduce cardiovascular mortality and combined cardiovascular events. However, studies had some risk of bias, and results were not always consistent, so additional higher-quality evidence is necessary to confirm these findings. Not enough evidence was available to establish whether influenza vaccination has a role to play in the primary prevention of cardiovascular disease.

PLAIN LANGUAGE SUMMARY

Flu vaccines for preventing cardiovascular disease

Flu infection may make cardiovascular disease (e.g. heart attack, stroke) and associated death more likely, and flu vaccination may reduce this risk. We included randomised studies comparing people receiving flu vaccine with those receiving no vaccine (placebo or no treatment). For this review update, we found eight trials studying 12,029 participants. Four of these studies examined patients with known heart disease (1682 participants), and the other four focused on the general population or elderly people (10,347 participants). The general population studies reported cardiovascular disease outcomes as part of their safety analyses, but the numbers of cases were too few to allow a judgement on whether flu vaccination was protective in these populations, and no differences were seen between groups. Overall, studies in people with heart disease suggest that flu vaccination may reduce death as a result of cardiovascular disease and may reduce combined cardiovascular disease events (such as heart attacks, strokes, necessity for bypass operations, etc.). However, these studies were small and had some risk of bias, so larger studies of better quality are needed to confirm the results.

BACKGROUND

This is an update of the original review published in 2008.

Description of the condition

Cardiovascular disease (CVD) remains the number one cause of death globally (WHO 2011a). Cardiovascular disease is the result of disorders of the heart and blood vessels and includes cerebrovascular disease, coronary heart disease (CHD) and peripheral arterial disease (PAD) (WHO 2011b). In 2008, an estimated 17.3 million people died from CVD, representing 30% of all global deaths. Of these deaths, an estimated 7.3 million were due to CHD and 6.2 million to stroke (WHO 2011a). More than 80% of CVD deaths occur in low- and middle-income countries, and the number of CVD deaths is expected to increase to 23.3 million by 2030 (Mathers 2006; WHO 2011a). These data demonstrate that new treatment modalities and better preventive strategies are needed.

Description of the intervention

Influenza vaccine is protective against influenza infection in healthy adults (Jefferson 2007), and large cohort studies have shown that influenza vaccination is effective in preventing morbidity and mortality in the community. Influenza vaccination reduces influenza-like disease, pneumonia and risk of death among elderly persons (Nichol 2007). Furthermore, a possible association has been shown between influenza vaccination and reduced all-cause death, heart attack and stroke (Nichol 2003). However, given the observational nature of these studies, the results are potentially prone to bias (Nelson 2007; Simonsen 2007). Generally, influenza vaccine is safe and well tolerated. Local reaction (soreness, redness, tenderness or swelling) at the site of injection is observed in 64% of vaccinated people. Red eyes, fever, runny nose, hoarse voice and cough have occasionally been reported. Rarely, influenza vaccine can cause allergic reactions (immediate hypersensitivity reactions) (Fiore 2010). No clear link

to Guillain-Barré syndrome (GBS) has been observed over many years of vaccine use. However, if any risk should occur, no more than one or two cases per million vaccinations would be expected (ACIP 2012). In the light of all risks and benefits, risk of a serious reaction to influenza vaccine is much less than risk of severe influenza disease, which can be prevented by vaccination. Influenza vaccine is considered a very safe product with many benefits, especially for members of high-risk groups.

How the intervention might work

Increased risk of cardiovascular disease during influenza infection has been shown in a large case series that used within-person comparisons (Smeeth 2004). Smeeth et al included 20,486 persons with first myocardial infarction and 19,063 persons with first stroke from the General Practitioner Database. They showed that, although no increase was seen after influenza vaccination, risk of acute cardiovascular events increased fivefold in the first three days after respiratory tract infection. In addition, risk of stroke increased threefold during this period. These findings suggest a causal role for acute infection triggering cardiovascular events. Warren-Gash 2009 carried out a systematic review of the evidence that influenza infection triggers acute myocardial infection and cardiovascular death. These review authors included 37 observational studies and two randomised controlled trials (RCTs). Observational studies showed a consistent association between influenza infection and myocardial infarction. Evidence of an association with cardiovascular death was weaker. Investigators found similar associations in two subsequent large observational studies from the UK and Hong Kong (Warren-Gash 2011; Warren-Gash 2012).

Various mechanisms have been proposed to explain why influenza infection may trigger cardiovascular events (Hebsur 2014; Rogers 2012). Although several infectious agents are thought to increase cardiovascular risk through a cascade of systemic infection and subsequent inflammation, the influenza virus may play a more specific role in triggering acute events by exclusively targeting areas of atherosclerosis and destabilising preexisting plaques. Other potential mechanisms include high-density lipoprotein, loss of anti-inflammatory properties, endothelial dysfunction, deposition of immune complexes in atherosclerotic plaques and elevation of macrophage circulation into the arteries.

Several studies have shown that influenza vaccination protects against acute coronary syndromes (Naghavi 2000; Nichol 2003; Siscovick 2000). In a large cohort study, Nichol and co-workers found that hospitalisation for acute coronary syndromes was reduced among participants who received influenza vaccination (Nichol 2003). During two consecutive seasons, more than 140,000 members of managed care organisations 65 years of age or older were studied. During two consecutive years, influenza vaccination reduced the risk of hospitalisation for cardiac disease by 19% and reduced the risk of hospitalisation for cerebrovascular disease by 16%. Therefore investigators concluded that influenza

vaccination was associated with reduced risk of heart disease and cerebrovascular disease during influenza season.

Why it is important to do this review

The observational nature of most studies makes it difficult to draw definitive conclusions, and many questions remain. Observational studies in this area may be prone to the following sources of bias: (1) “healthy user bias”, whereby ‘healthy’ people have higher vaccine uptake than ‘unhealthy’ people and are likely to exhibit a range of healthy behaviours and to have better health outcomes regardless of vaccination; (2) “frailty selection bias”, by which more frail people who are closer to death may be less likely to receive influenza vaccine than other people; and (3) apparent protective effects of influenza vaccine against death outside the influenza season, which are shown in some observational studies, suggesting residual biases or mechanisms other than influenza prevention.

In addition, the effectiveness of influenza vaccination is dependent on many factors including the age and immunity of recipients and the effectiveness of the vaccine. Indeed, influenza vaccination is most effective when the inactive influenza strains in the vaccine match the circulating strains in the community. In seasons with a poor match, the reduction in hospitalisation and death is smaller than in seasons with a good match (Nichol 2007).

Because effective influenza vaccines are cheap and widely available, use of influenza vaccination to prevent acute coronary syndromes is an appealing prevention strategy for those at risk. Whether influenza vaccination reduces cardiovascular disease remains not fully established. This systematic review assesses the effects of influenza vaccination in people with and without cardiovascular disease for the prevention of cardiovascular disease.

OBJECTIVES

To assess the potential benefits of influenza vaccination for primary and secondary prevention of cardiovascular disease.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) comparing influenza vaccination with placebo or no intervention when data on one of the outcomes was reported. We excluded all non-randomised controlled trials.

Types of participants

We included participants 18 years of age and older of either sex if influenza vaccination was given as a routine influenza prevention programme, as primary prevention of myocardial infarction and as secondary prevention. Participants may (secondary prevention) or may not (primary prevention) have had a history of CVD (stable or unstable angina, myocardial infarction, stroke or PAD). We included participants who were taking medication.

Types of interventions

Influenza vaccination (inactivated whole virus, detergent-treated split products or purified haemagglutinin and neuraminidase surface antigen formulation of the three influenza virus strains influenza A, B and C) administered by any route, at any dosage. We included studies comparing types, doses or schedules of influenza vaccine if one of the comparison groups received placebo or no intervention. Use of co-interventions was not an exclusion criterion if the same were used in different comparison groups.

Types of outcome measures

Trials had to report one of the following outcomes.

Primary outcomes

For patients without previous cardiovascular disease, the following were primary outcomes.

1. First-time myocardial infarction.
2. First-time unstable angina.
3. Death from cardiovascular causes.

For patients with previous cardiovascular disease, the following were primary outcomes.

1. Myocardial infarction.
2. Unstable angina.
3. Death from cardiovascular causes.

Secondary outcomes

We also considered related outcomes (e.g. composite clinical outcomes). It was noted whether cardiovascular outcomes were reported as primary outcomes and whether the vaccine was shown to be effective in reducing influenza infection.

Search methods for identification of studies

We developed the search strategy for this review in accordance with guidelines of the Cochrane Heart Group. We applied no language restrictions.

Electronic searches

We sought all RCTs of influenza vaccination compared with placebo or no intervention, using the following databases, on 18 October 2013.

1. The Cochrane Central Register of Controlled Trials (CENTRAL) (2013, Issue 9 of 12).
2. MEDLINE (Ovid, 1946 to 2013 October Week 1).
3. MEDLINE (PubMed, 20 February 2015).
4. EMBASE Classic + EMBASE (Ovid, 1947 to 2013 Week 41).
5. The Database of Abstracts of Reviews of Effects (DARE) (2013, Issue 3 of 4).
6. The Economic Evaluation Database (EED) (2013, Issue 3 of 4).
7. Health Technology Assessment (HTA) (2013, Issue 3 of 4).
8. Science Citation Index Expanded (SCI Expanded, 1970 to present) and Conference Proceedings Citation Index - Science (CPCI-S, 1990 to present) on Web of Science (Thomson Reuters).
9. Websites for ongoing trials: www.controlled-trials.com and www.clinicaltrials.gov (accessed 15 November 2014).

Search strategies for the specific databases searched in 2013 are listed in [Appendix 1](#). Search strategies from 2008 are provided in [Appendix 2](#). As the review update was broadened to CVD as compared with coronary heart disease, we have revised the search strategies for the update and have run the search without date limits.

The RCT filter for MEDLINE is the Cochrane sensitivity-maximising RCT filter, and for EMBASE, we applied terms recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2011). The RCT filter used for Web of Science is an adaptation of the Cochrane MEDLINE RCT filter.

Searching other resources

We searched reference lists of relevant primary studies and systematic reviews for further studies. We contacted the primary authors for additional information if necessary.

Data collection and analysis

Selection of studies

Two review authors (CC, NF) independently and systematically selected potentially eligible trials from the search. We excluded studies when they did not fulfil the inclusion criteria. If eligibility was unclear from the title/abstract of the record, we consulted the full-text article. We resolved discrepancies in selection between the two review authors by discussion.

Data extraction and management

Two review authors (CC, ZO) independently extracted data using a predefined review form. We extracted the following data systematically.

1. Trial characteristics: design, duration, country, setting.
 2. Intervention: type and method of vaccination, control intervention.
 3. Participants: inclusion and exclusion criteria, total number and numbers in comparison groups, baseline characteristics (age, sex, cardiovascular risk factors, cardiovascular medication), similarity of groups at baseline, withdrawals, losses to follow-up.
 4. Outcomes: primary and secondary outcomes as per trial, myocardial infarction or reinfarction, unstable angina, death from cardiovascular causes and related outcomes.
- We resolved discrepancies in data extraction by discussion.

Assessment of risk of bias in included studies

We assessed risk of bias in trials by using the Cochrane 'Risk of bias' tool, assessing the following criteria.

1. Random sequence generation (adequacy of method).
2. Allocation concealment.
3. Blinding of participants and personnel.
4. Handling of incomplete outcome data.
5. Dropouts/losses to follow-up.
6. Intention-to-treat analysis.
7. Selective reporting.
8. Similarity at baseline.
9. Any other bias noted.

Two review authors (CC, ZO) independently assessed risk of bias, and we resolved discrepancies by discussion.

Measures of treatment effect

All outcomes of interest were dichotomous outcomes and were presented as risk ratios (RRs) at the last reported follow-up.

Dealing with missing data

When substantial information was missing (e.g. trial information available only in abstract form), we contacted study authors to ask for further information.

Assessment of heterogeneity

We assessed heterogeneity by using the I^2 statistic and the Chi^2 statistic with significance levels set at P value = 0.1.

Data synthesis

We summarised data on cardiovascular death in a meta-analysis using the method of Mantel-Haenzel and a random-effects model. We plotted data on other cardiovascular outcomes for graphical representation, but we applied no summary statistics, as heterogeneity between studies was significant.

Subgroup analysis and investigation of heterogeneity

Potentially relevant subgroup analyses include the following.

1. Age (participants < 65 years or \geq 65 years).
2. Sex (male vs female).
3. General population versus population with established CVD.
4. Among participants with established heart disease, participants with acute coronary syndrome versus those with stable angina/elective percutaneous coronary intervention.
5. Studies reporting effective protection of the vaccination against influenza versus studies reporting less effective protection against influenza.

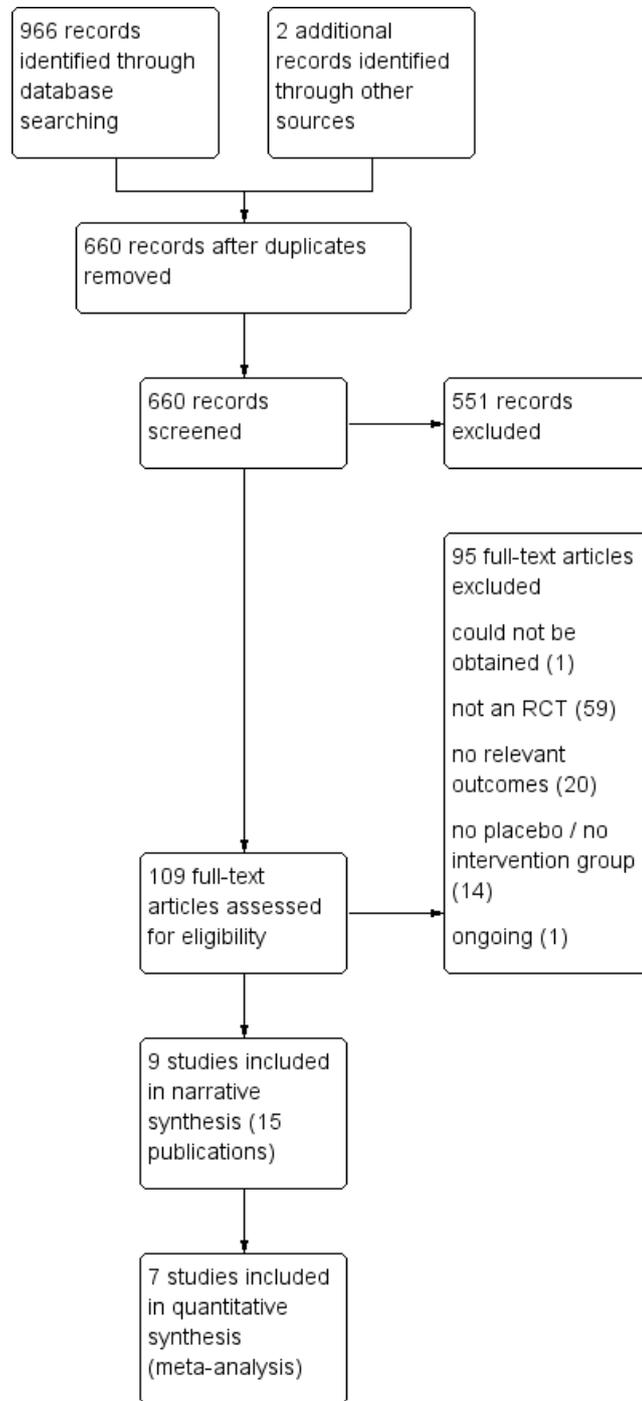
RESULTS

Description of studies

Results of the search

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) study flow diagram of the search for the updated and extended review is shown in [Figure 1](#). Electronic searches identified 966 records. On the basis of titles and abstracts, we excluded 550 records and we assessed 109 full-text records for eligibility.

Figure 1. Study flow diagram.



Of 109 records examined in full, we considered 13 to be eligible for inclusion, and we found two additional studies by searching the reference sections of relevant reviews and by updating our search of databases of ongoing trials. These 15 records represented nine independent studies (De Villiers 2009; FLUCAD 2008; FLUVACS 2002; Govaert 1994; IVCAD 2009; Langley 2011a; NCT01945268; Phrommintikul 2011; Wu 2010) (some of the 15 records were conference abstracts and have not been listed in the reference section). One of the trials was available in abstract form only (IVCAD 2009), but we obtained additional information by contacting the study author. Six of these trials reported cardiovascular death (FLUCAD 2008; FLUVACS 2002; Govaert 1994; IVCAD 2009; Langley 2011a; Phrommintikul 2011) and could be included in a meta-analysis of this outcome. Two had already been included in the previous version of the review (FLUCAD 2008; FLUVACS 2002), and the remainder were newly added.

Included studies

For details of the study characteristics of individual studies, see [Characteristics of included studies](#).

Study design

All included RCTs were parallel trials using individual randomisation. Four were multi-centre trials (De Villiers 2009; FLUVACS 2002; Govaert 1994; Langley 2011a). Trials were carried out in Argentina (FLUVACS 2002), China (Wu 2010), Iran (IVCAD 2009), North America (Langley 2011a), Poland (FLUCAD 2008), South Africa (De Villiers 2009), Thailand (Phrommintikul 2011) and the Netherlands (Govaert 1994). Follow-up was provided between 42 days and one year after vaccination.

Participants

Study participants fell within three main groups (n = 12,029 in total). The first group of studies (n = 5267 participants) comprised two RCTs including healthy adults over 18 years of age (Langley 2011a) or between 18 and 60 years of age (Wu 2010). In the study by Langley 2011a, adults with controlled chronic disease were eligible, but no information was provided as to what proportion of participants had chronic disease. Wu 2010 excluded participants with chronic disease. Participants in the study by Langley 2011a were between 18 and 91 years of age (mean age of participants younger than 65 years was around 39 years, and 72 years for participants 65 years of age or older), and mean age was around 42 years in the study by Wu 2010. Between 40% and 47% of participants were men.

The second group of two studies (n = 5080) included participants of 60 years of age or older (De Villiers 2009; Govaert 1994) with controlled chronic conditions. Participants were between 60 and

98 years of age, mean age was around 70 years in the study by De Villiers 2009 and most participants were between 60 and 74 years old in the study by Govaert 1994. Between 39% and 49% of participants were men. Between 13.5% and 16% had cardiac disease (undefined), and 2% to 9% had diabetes mellitus. In the study by De Villiers 2009, 50.5% of participants had hypertension.

The third group comprised four studies (n = 1682) including participants with known coronary artery disease (FLUCAD 2008; FLUVACS 2002; IVCAD 2009; Phrommintikul 2011) with variable age cutoffs (older than 21 to older than 50 years). FLUCAD 2008 and FLUVACS 2002 reported outcomes for subgroups of participants with acute myocardial infarction (MI) and those undergoing coronary revascularisation procedures. IVCAD 2009 also included these two groups of participants without distinguishing between subgroups, and the study by Phrommintikul 2011 included participants admitted to hospital with an acute coronary syndrome. Mean age of participants was between 58 and 67 years, and between 52% and 74% were men. Studies included participants with acute MI (with ST or non-ST segment MI) as well as those with coronary stenosis or angina and those undergoing revascularisation procedures. Details of the type of coronary artery disease, of cardiovascular comorbidities and of pharmacological therapy for cardiovascular conditions can be found in the [Characteristics of included studies](#).

Interventions

Details of the vaccines received can be found in [Characteristics of included studies](#). Six trials gave single injections of influenza vaccine, and two trials gave a second dose after 21 days (Langley 2011a; Wu 2010). Most trials compared one intervention group with a control group, and only Wu 2010 included six intervention groups with different doses of whole or split virion vaccines with or without aluminium hydroxide adjuvant. In most trials, the control group received placebo injections; one trial had a 'no intervention' control group (Phrommintikul 2011).

Outcome measures

For half of the trials, the primary focus was on prevention of influenza infection (influenza/influenza-like illness or immunogenicity) and cardiovascular outcomes were reported among the safety analyses (De Villiers 2009; Govaert 1994; Langley 2011a; Wu 2010); for the other half, the focus was on secondary cardiovascular prevention (FLUCAD 2008; FLUVACS 2002; IVCAD 2009; Phrommintikul 2011).

Cardiovascular outcomes reported in safety analyses included cardiovascular death, stroke and angina.

Three of the secondary prevention studies included cardiovascular death in their primary outcomes. Other outcomes were composite

outcomes (major adverse coronary event (MACE - composite of cardiovascular death, acute MI, coronary revascularisation); coronary ischaemic event (MACE or hospitalisation for myocardial ischaemia); double or triple endpoint of cardiovascular death, non-fatal MI or severe recurrent ischaemia; acute coronary syndrome (acute MI or unstable angina)), acute MI, stroke, heart failure and unstable angina or coronary revascularisation (percutaneous cardiac intervention (PCI) or coronary artery bypass graft (CABG)).

Protection against influenza

If cardiovascular adverse events are associated with influenza infection, it is important to show that the vaccines were really effective in preventing infection. Four studies reported that influenza infections were significantly reduced by the vaccination (De Villiers 2009; FLUCAD 2008; Govaert 1994; IVCAD 2009); three studies reported that the vaccines produced adequate seroprotection (IVCAD 2009; Langley 2011a; Wu 2010); one study reported that no cases of influenza were seen over the initial six-month follow-up in the intervention or the comparison group (FLUVACS 2002); and one study did not report on the effectiveness of the vaccination against influenza (Phrommintikul 2011).

Funding

All trials reported their source of funding. One trial was funded by industry (De Villiers 2009), three had mixed industrial and non-industrial funding (FLUCAD 2008; Langley 2011a; Wu 2010) and four reported only non-industrial funding (FLUVACS 2002; Govaert 1994; IVCAD 2009; Phrommintikul 2011).

Ongoing studies

The ongoing trial (NCT01945268) is a double-blind secondary prevention RCT carried out in Canada (see [Characteristics of ongoing studies](#)). Around 600 participants with heart disease (New York Heart Association functional class II, III and IV) are included, and the effects of influenza vaccination on major adverse vascular events are evaluated.

Excluded studies

We excluded 95 records for the following reasons: The study was not an RCT (n = 59), eligible outcomes were not reported (n = 20) or the study did not have a placebo or 'no intervention' group (n = 14). One record could not be obtained (but was unlikely to be an RCT) and one ongoing trial was identified (MacIntyre 2007), but contact with study authors suggested that the trial was abandoned and replaced by a case-control study.

Risk of bias in included studies

The overall risk of bias of included studies is shown in [Figure 2](#). Risk of bias for each individual study is shown in [Figure 3](#). None of the studies fulfilled all of the specified criteria. The three studies of highest quality had small deficits in one or two of the criteria (De Villiers 2009; FLUCAD 2008; Wu 2010), three studies had deficits in three or four of the criteria (Govaert 1994; Langley 2011a; Phrommintikul 2011) and two studies had deficits in more than half of the risk of bias criteria (FLUVACS 2002; IVCAD 2009).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

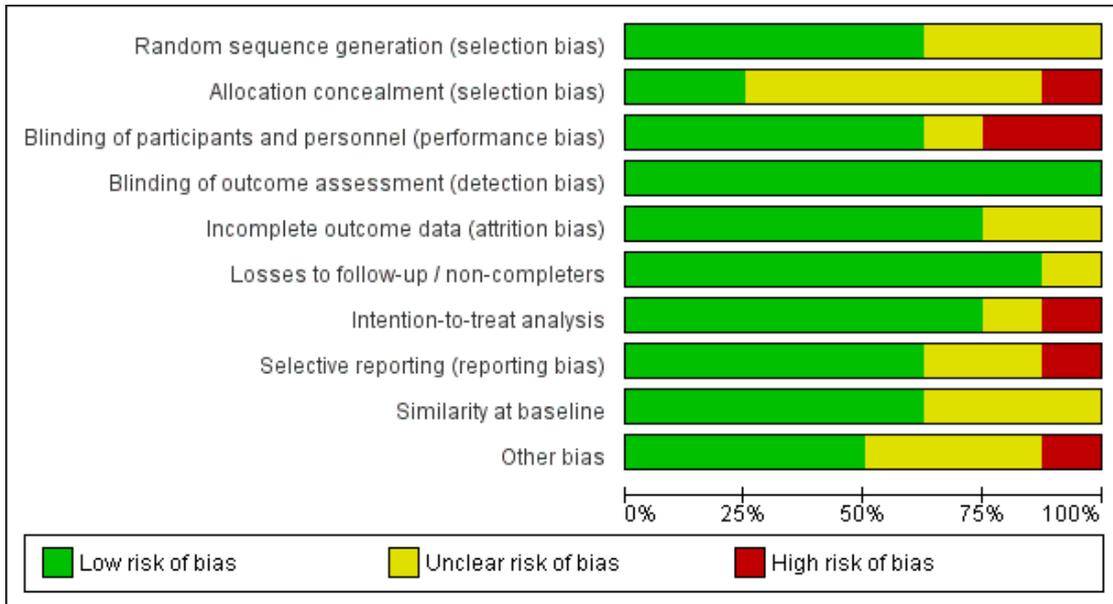


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Losses to follow-up / non-completers	Intention-to-treat analysis	Selective reporting (reporting bias)	Similarity at baseline	Other bias
De Villiers 2009	+	?	+	+	+	+	+	+	+	+
FLUCAD 2008	+	+	+	+	+	+	+	+	?	?
FLUVACS 2002	?	?	?	+	+	+	+	-	?	-
Govaert 1994	?	?	+	+	+	+	?	?	+	+
IVCAD 2009	?	-	-	+	?	+	-	?	+	?
Langley 2011a	+	?	+	+	?	?	+	+	+	+
Phrommintikul 2011	+	?	-	+	+	+	+	+	?	+
Wu 2010	+	+	+	+	+	+	+	+	+	?

Allocation

The randomisation process was clearly reported and adequate in five studies (De Villiers 2009; FLUCAD 2008; Langley 2011a; Phrommintikul 2011; Wu 2010); the others were unclear about method of randomisation. Only two studies had clearly adequate allocation concealment (FLUCAD 2008; Wu 2010).

Blinding

All of the studies reported blinding of outcome assessment. Participants and personnel were blinded in five trials (De Villiers 2009; FLUCAD 2008; Govaert 1994; Langley 2011a; Wu 2010). One trial did not clearly describe whether participants and personnel were blinded (FLUVACS 2002); in the IVCAD 2009 study, only participants were blinded; and in another study (Phrommintikul 2011), blinding was not possible as the control was 'no intervention'.

Incomplete outcome data

Attrition bias was adequately addressed in most trials, and two studies did not provide a clear description (IVCAD 2009; Langley 2011a). Dropouts and losses to follow-up were generally well balanced between comparison groups. The proportion of participants who completed the study ranged between 89% and 100% (over 95% for most studies). All but two studies (Govaert 1994; IVCAD 2009) clearly used intention-to-treat analysis.

Selective reporting

Most studies reported outcomes as outlined in the Methods section of the respective paper. The FLUVACS 2002 study reported on certain composite outcomes that were subsequently not reported, and some of the outcomes were only selectively reported in the subgroups assessed. Information on the IVCAD 2009 study was available only in abstract form and from information provided by the study author, so whether outcomes were reported as originally planned could not be assessed.

Other potential sources of bias

Most studies reported that comparison groups were balanced at baseline with respect to the most important characteristics. A difference in the proportion of participants taking calcium channel blockers at baseline may have been seen in the FLUCAD 2008 study (significance not reported). The authors of the FLUVACS 2002 study stated that groups were balanced with respect to age, sex and signs of necrosis (undefined), but some of the other parameters reported look less well balanced (e.g. hypertension, distribution of types of MI). In the study by Phrommintikul 2011,

a small significant difference was observed in participants taking angiotensin-converting enzyme (ACE) inhibitors/angiotensin II receptor blockers at baseline. Wu 2010 reported a limited number of baseline characteristics.

A power analysis was carried out and power was adequate in the following studies: De Villiers 2009; FLUCAD 2008; Langley 2011a; Phrommintikul 2011. A power analysis was carried out in the FLUVACS 2002 study, but the actual number of participants suggests that the study was underpowered for measuring the primary outcome.

Effects of interventions

Cardiovascular death

Cardiovascular death was reported by all secondary prevention studies and by three of the studies reporting mortality as part of their safety analyses. Overall analyses for cardiovascular death are shown in Analysis 1.2.

In the secondary prevention studies, significantly fewer cardiovascular deaths occurred in the vaccine group than in the control group (risk ratio (RR) 0.45, 95% confidence interval (CI) 0.26 to 0.76, P value 0.003) with no significant heterogeneity between studies. Cardiovascular death occurred in 2.3% of participants in the vaccine groups and in 5.1% of those in the control groups. Among individual studies, only FLUVACS 2002 reported a significantly lower cardiovascular death rate in the vaccine group than in the placebo group (6.2% vs 17.7%, P value 0.002) at one year; this was not maintained at two-year follow-up (P value 0.14). Among subgroups of participants with acute coronary syndromes/MI and those with stable angina/percutaneous cardiac interventions in the FLUCAD 2008 and FLUVACS 2002 studies, no significant difference in cardiovascular death was seen in either of the subgroups overall.

In studies reporting cardiovascular death as part of their safety analyses, no significant difference in cardiovascular death was observed between vaccine and placebo groups. Cardiovascular death occurred in 0.7% of participants in the vaccine groups and in 0.8% of participants in the placebo groups.

The outcome reported by De Villiers 2009 was death from all causes; the distribution of causes of death was not given for the comparison groups, but study authors stated that the most frequent causes of death were MI, cardiac failure and cerebrovascular disorders, and that these occurred in statistically similar proportions of vaccine and placebo recipients (all P values \geq 0.422; Analysis 1.1).

Other cardiovascular outcomes

[Analysis 1.4](#) to [Analysis 1.14](#) show results for other cardiovascular events as reported by study investigators.

Studies targeting a reduction in cardiovascular events reported a range of cardiovascular outcomes.

In the [FLUCAD 2008](#) study, no significant differences in major adverse coronary events (MACE - cardiovascular death, MI or coronary revascularisation) over 12 months were reported in the vaccine group compared with the placebo group (3.00% vs 5.87%, P value 0.13; [Analysis 1.3](#)). However, the rate of coronary ischaemic events (MACE or hospitalisation for myocardial ischaemia) over 12 months was significantly lower in the vaccine group than in the placebo group (6.02% vs 9.97%, P value 0.047; [Analysis 1.4](#)). This applied to the participant population overall and to the subgroup with an acute coronary syndrome, but no significant difference in coronary ischaemic events was noted in the subgroup with stable angina. No significant difference was reported between groups in terms of individual cardiac events, namely, cardiovascular death, MI (ST segment elevation MI (STEMI) or non-ST segment elevation MI (NSTEMI)), coronary revascularisation or hospitalisation for myocardial ischaemia (see [Analysis 1.15](#); [Analysis 1.10](#); [Analysis 1.14](#)). This applied to the participant population overall and to both subgroups (those with an acute coronary syndrome and those with stable angina). Multi-variate analyses identified female sex (hazard ratio (HR) 2.15, 95% CI 1.11 to 4.15%, P value 0.024) and recent acute coronary syndrome (HR 2.93, 95% CI 1.52 to 5.65, P value 0.001) as predictors of coronary ischaemic events, and influenza vaccination was found to be protective (HR 0.38, 95% CI 0.19 to 0.78, P value 0.009). No effects were seen for age, smoking, hypertension, elevated low-density lipoprotein (LDL)-cholesterol, low high-density lipoprotein (HDL)-cholesterol or presence of diabetes mellitus.

In the [FLUVACS 2002](#) study (see [Analysis 1.5](#); [Analysis 1.6](#); [Analysis 1.15](#); [Analysis 1.10](#); [Analysis 1.14](#)), the triple endpoint (acute MI, rehospitalisation for recurrent angina, death) was seen less frequently in the vaccine group than in the placebo group for the whole population (RR 0.50, 95% CI 0.29 to 0.85, P value 0.009) and in the subgroup with acute MI (RR 0.42, 95% CI 0.21 to 0.83, P value 0.008) but not for the PCI stenting subgroup at six months. No significant difference in MI was reported in either subgroup. Also no significant differences in cardiac revascularisation were noted in the PCI stenting group. Among participants with acute MI, significantly fewer were rehospitalised for ischaemia in the vaccine group (RR 0.33, 95% CI 0.11 to 1.0, P value 0.03), and significantly fewer participants had a double endpoint (of reinfarction, hospitalisation for ischaemia and death) (RR 0.30, 95% CI 0.22 to 1.28, P value 0.03). These results were largely maintained at one-year follow-up. In the whole study group, 22% of participants had a triple endpoint in the vaccine group and 37% in the placebo group (RR 0.59, 95% CI 0.4 to 0.86, P value 0.004). The difference was also significant in the subgroup with acute MI at one year (19% vs 42%, RR 0.44, 95% CI 0.27 to 0.71, P value

0.0003) but not in the PCI stenting group. Significant benefit of the vaccination for occurrence of the double endpoint was seen only in the MI subgroup (10% vs 28%, RR 0.37, 95% CI 0.19 to 0.72, P value 0.002), not in the whole study population. No significant difference in MI or rehospitalisation for ischaemia was seen. Cox regression analyses were done for the combined triple endpoint at one year for the following subgroups: participants older or younger than 65 years, those with ST segment elevation or non-ST segment elevation MI, participants with elevation or no elevation of enzymes at entry, those with diabetes or no diabetes, participants with a history or no history of smoking, those with thrombolysis in myocardial infarction (TIMI) risk score below or above 6 and participants with a history or no history of revascularisation. Significantly greater benefit with influenza vaccination was seen among participants with non-ST segment elevation MI (RR 0.13, 95% CI 0.03 to 0.52, P value 0.004), those older than 65 years (RR 0.36, 95% CI 0.14 to 0.92, P value not given), non-smokers (RR 0.18, 95% CI 0.05 to 0.57, P value not given) and those at high risk for future ischaemic episodes (TIMI risk score > 6) (RR 0.22, 95% CI 0.06 to 0.87, P value not given).

The [IVCAD 2009](#) study reported no significant differences between the vaccination group and the placebo group in individual cardiovascular outcomes over one year (CABG, PCI, MI, episodes of unstable angina, cardiovascular death; see [Analysis 1.8](#); [Analysis 1.9](#); [Analysis 1.10](#); [Analysis 1.13](#)). Significantly more participants with at least one cardiac adverse event (acute coronary syndrome, coronary revascularisation, cardiovascular death) were reported in the placebo group than in the vaccine group at six months, but this finding was not maintained at one-year follow-up (29% in the intervention group vs 26% in the placebo group, P value 0.6; [Analysis 1.7](#)). Study authors also reported that angina severity scores were more improved in the vaccine group than in the placebo group.

In the study by [Phrommintikul 2011](#) (see [Analysis 1.3](#); [Analysis 1.11](#); [Analysis 1.12](#); [Analysis 1.14](#)), participants in the vaccine group had significantly fewer major adverse coronary events (MACE, composite of cardiovascular death or hospitalisation for acute coronary syndrome, heart failure or stroke) at 12 months than did participants in the placebo group (9.5% vs 19.3%, unadjusted HR 0.70, 95% CI 0.57 to 0.86, P value 0.004). The rate of hospitalisation for acute coronary syndrome was also significantly lower in the vaccine group than in the placebo group (4.5% vs 10.6%, unadjusted HR 0.73, 95% CI 0.55 to 0.91, P value 0.032). Effects for these two outcomes remained significant with adjustments for age, sex, serum creatinine, ACE inhibitor treatment and coronary revascularisation. No significant difference was reported for cardiovascular death, hospitalisation for heart failure or hospitalisation for stroke. No significant difference in effects for MACE was observed for the following subgroups: participants younger than 65 years or older than 65 years, male or female participants, those with or without diabetes mellitus, participants with ST segment elevation or non-ST segment elevation MI, those with serum

creatinine levels less than 1.1 mg/dL or greater than 1.1 mg/dL and participants with or without revascularisation. Limited information on non-fatal cardiovascular adverse events was reported by studies that included cardiovascular events in their safety analyses. [Govaert 1994](#) reported three cases of 'intercurrent illness (undefined), cerebrovascular accident' - two in the placebo group (0.2%) and one in the vaccine group (0.1%) (RR 0.49, 95% CI 0.04 to 5.41). [Wu 2010](#) reported five cases of angina in the intervention groups (0.8%) and none in the placebo groups (RR 1.83, 95% CI 0.1 to 32.85).

Adverse events

[De Villiers 2009](#) reported that more reactogenicity events (including runny nose/nasal congestion, cough, sore throat, headache, muscle aches, tiredness and decreased appetite) occurred in the vaccine group 11 days after vaccination (P value 0.042). No significant differences in serious adverse events were observed between vaccination and placebo groups over four weeks (1% vs 1.5%, P value 0.27) or eight months (10.1% vs 8.6%) post vaccination. In the study by [Langley 2011a](#), no significant differences were observed between vaccine and placebo groups over one year in reporting of one or more serious adverse events (3.2% vs 4.0%) or reporting of one or more medically attended events (30% vs 30.4%).

[Wu 2010](#) reported the following rates of adverse events for the different intervention groups over 42 days: whole virion + Al 5 µg 12.9%, whole virion + Al 10 µg 19.6%, split virion + Al 7.5 µg 14.9%, split virion + Al 15 µg 12.0%, split virion 15 µg 7.9%, split virion 30 µg 11.9% and placebo 7.0%. The highest rate was seen with whole virion + Al 10 µg vaccine (P value 0.016 vs whole virion + Al 15 µg), but no significant association with dosage, presence of aluminium adjuvant or type of vaccine (whole virion vs split virion) was described. The rate of mild adverse events ranged between 5.0% and 17.6%, that of moderate adverse events between 0 and 2.0% and that of severe adverse events between 0 and 1%.

No adverse events beyond the cardiovascular outcomes already summarised were reported in the following studies: [FLUCAD 2008](#), [Govaert 1994](#), [IVCAD 2009](#) and [Phrommintikul 2011](#).

DISCUSSION

Summary of main results

We included eight trials of influenza vaccination compared with placebo or no vaccination, with 12,029 participants receiving at least one vaccination or control treatment. Four of these trials (n = 10,347) focused on prevention of influenza in general or elderly populations and reported cardiovascular outcomes among their

safety analyses, and four trials (n = 1682) focused on prevention of cardiovascular events among participants with established coronary heart disease. Follow-up was between 42 days and one year. When reported (seven studies), vaccination provided adequate immunogenicity or protection against influenza. Cardiovascular mortality was reported by four secondary prevention trials and was significantly reduced by influenza vaccination (risk ratio (RR) 0.45, 95% confidence interval (CI) 0.26 to 0.76, P value 0.003) with no significant heterogeneity between studies. In three trials reporting cardiovascular mortality as part of their safety analyses, no differences were found between study groups, but numbers of events were too small to permit conclusions. Among studies of participants with coronary heart disease, composite outcomes of cardiovascular events also tended to be decreased with influenza vaccination compared with placebo. Generally no significant difference was observed between comparison groups regarding individual outcomes such as myocardial infarction.

Overall completeness and applicability of evidence

As the main focus of the general population studies including cardiovascular events in their safety analyses was not cardiovascular prevention, these studies were most likely underpowered for assessing cardiovascular events. Often reporting of cardiovascular death and of details on non-fatal cardiovascular events was very limited. Studies of participants with coronary heart disease generally included small sample sizes (around 100 to 150 participants per comparison group in most), often without power analyses or with clear evidence that they were underpowered.

Quality of the evidence

Moderate risk of bias was seen, with five RCTs showing deficits in at least three of the risk of bias criteria assessed. This included three studies of participants with coronary artery disease, and only one of these studies was rated as having low risk of bias ([FLUCAD 2008](#)).

Potential biases in the review process

This review included only randomised controlled trials (RCTs) conducted to assess effects of influenza vaccination on cardiovascular events. Given that these events are rare, especially in primary prevention trials, future updates of the review may benefit from more detailed examination of observational data on the association between influenza vaccination and prevention of cardiovascular events.

Agreements and disagreements with other studies or reviews

We identified two other systematic reviews of the association between influenza vaccination and cardiovascular outcomes (Loomba 2012; Udell 2013). Loomba 2012 summarised three RCTs and two observational studies including a total of 292,383 participants. Included studies examined participants with cardiovascular disease and mixed populations with and without cardiovascular disease. Overall, their meta-analyses showed a significant reduction in all-cause mortality (odds ratio (OR) 0.61, 95% CI 0.57 to 0.64), MI (OR 0.73, 95% CI 0.57 to 0.93) and major adverse cardiovascular events (OR 0.47, 95% CI 0.29 to 0.74). The review had some quality deficits, and results should be viewed with caution.

The systematic review by Udell 2013 was of higher quality. The review authors included RCTs (sample size of at least 50) of adults comparing experimental or commercially approved influenza vaccinations with placebo, no vaccination or another vaccination strategy. The same four trials of participants with coronary artery disease examining cardiovascular outcomes were included as in the present review (FLUCAD 2008; FLUVACS 2002; IVCAD 2009; Phrommintikul 2011), along with two of the studies including cardiovascular events in their safety analyses (De Villiers 2009; Govaert 1994), as well as safety analyses of six RCTs comparing different vaccine formulations. A meta-analysis of five RCTs (three of participants with coronary artery disease and two with cardiovascular events in their safety analyses) showed a significant reduction in composite cardiovascular events with influenza vaccination compared with control (2.9% vs 4.7%, RR 0.64, 95% CI 0.48 to 0.86, P value 0.003). When cardiovascular mortality was examined in the same five trials, no significant effect was seen overall (RR 0.81, 95% CI 0.36 to 1.83, P value 0.61). The greatest effects of the vaccine were seen among participants at highest risk with more active coronary disease. These results are consistent with those of the present review.

Findings of this review are in line with international recommendations for practice. Patients with chronic heart disease are generally believed to be at high risk for influenza infection, and different guidelines highly recommend use of influenza vaccine in these groups.

The current influenza vaccination guideline in the UK recommends annual influenza vaccination for patients with chronic heart disease, including those with congenital heart disease, hypertension with cardiac complications or chronic heart failure, and for individuals requiring regular medication and/or follow-up for ischaemic heart disease (UK Dept of Health 2014/15). Both the European Centre for Disease Prevention and Control (ECDC) and the US Centers for Disease Control and Prevention (CDC) recommend influenza vaccination for individuals with chronic car-

diovascular diseases such as congenital heart disease, congestive heart failure and coronary artery disease (CDC Europe 2014/15; CDC USA 2015).

The World Health Organization (WHO) categorises patients with cardiac diseases (atherosclerotic heart disease, cardiomyopathy/chronic congestive heart failure and congenital heart disease) in the high-risk group and recommends annual influenza vaccination in accordance with resources available in each country (WHO 2012).

AUTHORS' CONCLUSIONS

Implications for practice

Available RCTs did not provide enough information to show the effectiveness of influenza vaccination in the primary prevention of cardiovascular death or non-fatal cardiovascular events. In patients with established cardiovascular disease, limited evidence suggests that influenza vaccination may reduce cardiovascular mortality and combined cardiovascular events.

Implications for research

Future studies of primary and secondary prevention of cardiovascular events by influenza vaccination must be adequately powered to measure these outcomes and must observe other established quality criteria. Studies should be carried out in populations with established cardiovascular risk factors (e.g. hyperlipidaemia, hypertension, diabetes mellitus, obesity) to determine the effects of influenza vaccination in the primary prevention of cardiovascular disease - not just among inpatients with established cardiovascular disease. In general population studies, subgroups of participants with cardiovascular risk factors and subgroups of elderly participants (e.g. 65 years or older) should be examined with respect to cardiovascular events.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

De Villiers 2009

Methods	<p>Setting: South Africa; 31 sites</p> <p>Design: individual randomisation, parallel-group, double-blind</p> <p>Dates and follow-up: trial dates April 2, 2001 to November 30, 2001; follow-up 6.5 to 8 months after vaccination</p>	
Participants	<p>N: 3242 (1567/1620 completers in the intervention group and 1569/1622 in the control group)</p> <p>Inclusion criteria: community-dwelling ambulatory adults, ≥ 60 years, including individuals with any condition or disease not requiring a change in therapy or hospitalisation within 12 weeks before study vaccination</p> <p>Age: <i>intervention:</i> 69.5 SD 6.9 years (range 60 to 98); <i>control:</i> 69.6 SD 6.9 years (range 60 to 96)</p> <p>Sex (% men): <i>intervention:</i> 39.2%; <i>control:</i> 39.8%</p> <p>Ethnicity: <i>intervention:</i> 69.5% white, 29.8% African descent, 0.7% other; <i>control:</i> 69.5% white, 29.5% African descent, 1% other</p> <p>Cardiovascular risk status: 50.5% hypertension, 16.2% cardiac disease, 9.4% diabetes mellitus - no details on group distribution</p>	
Interventions	<p>Intervention (n = 1620): 1 dose of live attenuated influenza vaccine (Wyeth Vaccines Research); each 0.2 mL dose contained approximately 10^7 median tissue culture infectious doses or equivalent fluorescent focus units of each 6:2 reassortant virus strain; haemagglutinin and neuraminidase antigens of wild-type influenza strains used to generate type A/H1N1 and A/H3N2 vaccine reassortants were antigenically representative of those recommended by the WHO for the 2001 Southern Hemisphere influenza season: A/New Caledonia/20/99 (H1N1) and A/Panama/2007/99 (H3N2); because of technical problems in production, the recommended type B vaccine component, B/Sichuan/379/99-like virus, was replaced with B/Yamanashi/166/98 (Beijing-like) virus in the study vaccine</p> <p>Control (n = 1622): sterile physiological saline manufactured by Wyeth</p>	
Outcomes	<p>Primary outcomes: culture-confirmed influenza attack</p> <p>Secondary outcomes: adverse effects, deaths associated with cardiovascular and/or respiratory causes</p> <p>Did the intervention group have significantly lower risk of influenza? Yes</p>	
Funding / conflict of interest	Study funded by manufacturer (Wyeth Research)	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement

De Villiers 2009 (Continued)

Random sequence generation (selection bias)	Low risk	Randomisation schedule was created by Wyeth Vaccines Research
Allocation concealment (selection bias)	Unclear risk	No details were given
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study participants and those administering the interventions were blinded to group assignment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were blinded to group assignment; relationships of adverse events to study product were assessed before study unblinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low attrition; participants receiving vaccine were included in the safety analysis
Losses to follow-up / non-completers	Low risk	Intervention group: 53/1620 (3.3%) Control group: 53/1622 (3.3%)
Intention-to-treat analysis	Low risk	All participants who received a dose of vaccine were included in the safety analyses
Selective reporting (reporting bias)	Low risk	All outcomes were reported as specified
Similarity at baseline	Low risk	Groups were balanced at baseline (not reported for underlying conditions)
Other bias	Low risk	Power analysis for vaccine efficacy was performed

FLUCAD 2008

Methods	<p>Setting: Poland; single-centre; inpatients vaccinated within 1 week of coronary intervention before discharge from the hospital; outpatients vaccinated during office visits to cardiologist</p> <p>Design: individual randomisation, parallel-group, double-blind</p> <p>Dates and follow-up: recruitment October 2004 to February 2005; trial dates October 2004 to December 2005; median follow-up time 298 days (range 4 to 370 days, measured to first event or end of observation period)</p>
Participants	<p>N: 658 (325/352 completers in the intervention group; and 333/333 in the control group)</p> <p>Inclusion criteria: patients aged 30 to 80 years with coronary artery disease confirmed by angiography with $\geq 50\%$ stenosis of ≥ 1 large epicardial coronary artery</p> <p>Age: <i>intervention:</i> 58.8 years (range 35 to 80); <i>control:</i> 58.1 years (range 32 to 80)</p> <p>Sex (% men): <i>intervention:</i> 71.1%; <i>control:</i> 73.9%</p>

	<p>Ethnicity: not reported</p> <p>Cardiovascular risk status: <i>intervention:</i> 69.7% hypertension, 19.8% diabetes mellitus, history of...: 64.6% myocardial infarction, 52.3% percutaneous coronary interventions, 11.7% coronary bypass, 2.2% atrial fibrillation, 4.6% stroke, 12.9% heart failure; <i>control:</i> 63.4% hypertension, 20.7% diabetes mellitus, history of...: 69.7% myocardial infarction, 56.5% percutaneous coronary intervention (PCI), 13.8% coronary bypass, 2.4% atrial fibrillation, 4.5% stroke, 15.9% heart failure</p> <p>Type of acute coronary syndrome: <i>intervention:</i> 44.6% recent intervention (25.5% primary PCI (14.1% STEMI, 8.0% NSTEMI, 3.4% unstable angina, 10.1% abciximab), 19.1% elective PCI), 55.4% ambulatory coronary artery disease; <i>control:</i> 42.9% recent intervention (22.2% primary PCI (10.5% STEMI, 5.1% NSTEMI, 6.6% unstable angina, 7.2% abciximab), 20.7% elective PCI), 57.1% ambulatory coronary artery disease</p> <p>Pharmacological therapy: <i>intervention:</i> 97.9% aspirin, 49.9% thienopiridines, 99.1% statins, 93.5% β-blockers, 91.1% ACE inhibitors, 27.1% calcium blockers, 18.3% nitrates, 21.2% diuretics, 15.7% oral antihyperglycaemics, 5.5% insulin <i>control:</i> 97.3% aspirin, 47.2% thienopiridines, 97.9% statins, 94.9% β-blockers, 94.0% ACE inhibitors, 18.0% calcium blockers, 15.4% nitrates, 24.9% diuretics, 16.2% oral antihyperglycaemics, 4.8% insulin</p>	
Interventions	<p>Intervention group (n = 325): single-dose intramuscular injection of 0.5 mL (15 μg) of inactivated subunit influenza vaccine containing haemagglutinin of each of the following strains: A/NewCaledonia/20/99 (H1N1), A/Christchurch/28/03 (H3N2), B/Jiangsu/10/03</p> <p>Control group (n = 333): placebo containing vaccine components except viral antigens</p>	
Outcomes	<p>Primary outcomes: cardiovascular death within 12 months of vaccination</p> <p>Secondary outcomes: major adverse cardiac event (MACE) (composite of: cardiovascular death, acute myocardial infarction (MI), or coronary revascularisation (PCI or coronary bypass)), and coronary ischaemic event (MACE or hospitalisation for myocardial ischaemia) at 12 months), coronary revascularisation, hospitalisation for myocardial ischaemia, myocardial infarction, adverse events</p> <p>Did the intervention group have significantly lower risk of influenza? Yes</p>	
Funding / conflict of interest	<p>Main funding was non-industrial (grant from Polish Ministry of Education and Science), vaccine and placebo provided by Solvay Pharmaceuticals B.V</p>	
Notes		
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	1:1; computer-generated by an independent statistician
Allocation concealment (selection bias)	Low risk	Identical syringes with vaccine or placebo were labelled with randomisation numbers by persons not involved in the study, then

FLUCAD 2008 (Continued)

		were delivered to the site
Blinding of participants and personnel (performance bias) All outcomes	Low risk	See above
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Randomisation code remained with the independent ethics committee until the database was closed
Incomplete outcome data (attrition bias) All outcomes	Low risk	No attrition
Losses to follow-up / non-completers	Low risk	Intervention group: none Control group: none
Intention-to-treat analysis	Low risk	For all outcomes
Selective reporting (reporting bias)	Low risk	All outcomes were reported as specified
Similarity at baseline	Unclear risk	Groups look well balanced; possible baseline difference in calcium blockers?
Other bias	Unclear risk	Power analysis with 80% power for MACE incidence

FLUVACS 2002

Methods	<p>Setting: Argentina; 6 care units Design: individual randomisation, parallel-group Dates and follow-up: recruitment May to early September 2001; primary endpoint 6 months, follow-up 1 year</p>
Participants	<p>N: 301 (194/200 completers in the MI group and 98/101 in the PCI group) Inclusion criteria: > 21 years; 2 groups: (1) patients with ST segment elevation myocardial infarction (MI) or non-ST segment MI occurring during the previous 72 hours; (2) patients undergoing angioplasty/stenting (PCI) Age: <i>intervention:</i> MI/PCI 64 years; <i>control:</i> MI 66 years, PCI 63 years Sex (% men): <i>intervention:</i> MI 65%, PCI 72%; <i>control:</i> MI 73%, PCI 70% Ethnicity: not reported Cardiovascular risk status: <i>intervention:</i> MI group 56% hypertension, 20% diabetes mellitus, 14% prior MI, 42% current/former smoker, 14% bypass or PCI; PCI group 59% hypertension, 47% current/former smoker, 16% diabetes mellitus, 59% hypercholesterolaemia; <i>control:</i> MI group 33% hypertension, 30% current/former smoker, 19% diabetes mellitus, 14% prior MI, 23% bypass or PCI; PCI group 68% hypertension, 66% current/former smoker, 12% diabetes mellitus, 56% hypercholesterolaemia Pharmacological therapy: <i>PCI patients at time of procedure:</i> Gp IIb/IIIa receptor antagonists: 6% in each group; all on aspirin plus clopidogrel; <i>survival patients at 1 year:</i> all on aspirin, 64% beta-blockers, 57% ACE inhibitors, 34%</p>

	statins; no difference in terms of medical therapy between groups at 1 year	
Interventions	<p>Intervention group (n = 100 MI, 51 PCI): single-dose intramuscular injection of 0.5 mL containing A/Moscow/10/99-like virus, A/New Caledonia/20/99 (H1N1)-like virus and AB/Sichuan/379/99-like virus</p> <p>Control group (n = 100 MI, 50 PCI): saline</p>	
Outcomes	<p>Primary outcomes: cardiovascular death</p> <p>Secondary outcomes: double endpoint or triple endpoint of cardiovascular death, non-fatal MI or severe recurrent ischaemia; acute myocardial infarction, rehospitalisation</p> <p>Did the intervention group have significantly lower risk of influenza? Stated that no influenza disease was reported in the different participant groups during the first 6-month follow-up</p>	
Funding / conflict of interest	Favaloro Foundation	
Notes		
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Stated to be single-blind, but that could refer to outcome assessment below?
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Data monitoring team was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low attrition rate; ITT analysis
Losses to follow-up / non-completers	Low risk	6/200 (3%) lost to follow-up in the MI group and 3/101 (3%) in the PCI group; not reported for intervention/control
Intention-to-treat analysis	Low risk	ITT analysis for all outcomes
Selective reporting (reporting bias)	High risk	Partially; time to triple end point not reported; selective reporting of outcomes for whole group or MI/PCI subgroups

Similarity at baseline	Unclear risk	Groups balanced at baseline with regards to age, sex and signs of necrosis, but some of the other parameters look less balanced
Other bias	High risk	Underpowered - stated that 4000 participants would have been needed for 80% power for primary endpoint (301 participants included)

Govaert 1994

Methods	<p>Setting: The Netherlands; 34 family physicians in 15 practices</p> <p>Design: individual randomisation, parallel-group, double-blind</p> <p>Dates and follow-up: study conducted winter 1991-1992; follow-up up to 5 months after vaccination</p>
Participants	<p>N: 1838 (902/927 completers in the intervention group and 889/911 in the control group)</p> <p>Inclusion criteria: aged \geq 60 years; not belonging to those high-risk groups in which vaccination had been given previously (heart or lung conditions, diabetes mellitus, chronic renal insufficiency, chronic staphylococcal infections - but interpreted differently by different family physicians)</p> <p>Age: <i>intervention:</i> 39.7% 60 to 64 years, 30.3% 65 to 69 years, 19% 70 to 74 years, 7.1% 75 to 79 years, 3.1% 80 to 84 years, 0.8% 85 to 91 years; <i>control:</i> 43.5% 60 to 64 years, 27.3% 65 to 69 years, 19.4% 70 to 74 years, 6.7% 75 to 79 years, 2.1% 80 to 84 years, 1% 85 to 91 years</p> <p>Sex (% men): <i>intervention:</i> 45.3%; <i>control:</i> 49.3%</p> <p>Ethnicity: not reported</p> <p>Previously vaccinated: <i>intervention:</i> 12.7%; <i>control:</i> 13.2%</p> <p>Cardiovascular risk status: <i>intervention:</i> 13.5% cardiac disease, 2.3% diabetes mellitus; <i>control:</i> 13.6% cardiac disease, 2.2% diabetes mellitus</p>
Interventions	<p>Intervention (n = 927): single injection of split-virus vaccine (Evans Medical Ltd, Langhurst, Horsham, England) in accordance with WHO advice; each 0.5 mL dose contained A/Singapore/6/86(H1N1), A/Beijing/353/89(H3N2), B/Beijing/1/87 and B/Panama/45/90, all with 15 μg of haemagglutinin</p> <p>Control (n = 911): physiological saline solution</p> <p>Did the intervention group have significantly lower risk of influenza? Yes</p>
Outcomes	<p>Primary outcomes: efficacy of vaccination against influenza (presenting with influenza-like illness, self reported influenza, serological influenza) (up to 5 months post vaccination)</p> <p>Secondary outcomes: morbidity and mortality (including cardiovascular causes)</p>
Funding / conflict of interest	No industrial funding, study supported by Prevention Fund; conflicts of interest not reported
Notes	

<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised in risk strata (cardiac disease, pulmonary disease, diabetes mellitus, other conditions, healthy); randomisation method not stated
Allocation concealment (selection bias)	Unclear risk	Method not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Visually similar syringes for vaccine and placebo; vaccination teams consisted of a family physician not belonging to the participating practices, an assistant to take the blood sample and an assistant to administer the vaccine
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Questionnaires regarding influenza-like illness were analysed by researchers blinded to vaccination status; serum samples were analysed by remote centre
Incomplete outcome data (attrition bias) All outcomes	Low risk	Participants with incomplete samples were retained in the analyses when possible; adverse events were reported for all
Losses to follow-up / non-completers	Low risk	Intervention group: 25/927 (2.7%) Control group: 22/911 (2.4%)
Intention-to-treat analysis	Unclear risk	Not reported
Selective reporting (reporting bias)	Unclear risk	All expected outcomes were reported but for relevant outcomes not enough details were reported regarding distribution between groups (e.g. for stroke, myocardial infarction)
Similarity at baseline	Low risk	Groups similar at baseline
Other bias	Low risk	

IVCAD 2009

Methods	<p>Setting: Iran; medical centre, inpatient and outpatient</p> <p>Design: individual randomisation, parallel-group</p> <p>Dates and follow-up: recruitment January to August 2008; follow-up until August 2009, participant followed for 6 months (abstract), detailed unpublished results for 1 year follow-up</p>	
Participants	<p>N: 278 (135/141 completers in the intervention group and 131/137 in the control group)</p> <p>Inclusion criteria: adults \geq 25 years with stable angina and confirmed coronary artery stenosis (by angiography) or acute, evolving or recent myocardial infarction (after recovering from the acute phase)</p> <p>Age: <i>intervention:</i> 54.9 SD 9.0 years; <i>control:</i> 54.5 SD 9.2 years</p> <p>Sex (% men): <i>intervention:</i> 66%; <i>control:</i> 67%</p> <p>Ethnicity: not reported</p> <p>Cardiovascular risk status: <i>intervention:</i> 82% hypertension, 83% hyperlipidaemia, all had coronary artery disease; <i>control:</i> 84% hypertension, 90% hyperlipidaemia, all had coronary artery disease</p>	
Interventions	<p>Intervention group (n = 141): intramuscular injection of one 0.5-mL dose of influenza vaccine; the vaccine contained 15 μg haemagglutinin of each of the 3 strains: Solomon Islands/3/2006 (H1N1), Wisconsin/ 67/2005 (H3N2) and Malaysia/2506/2004 (B) according to WHO guidelines for the anti-influenza vaccination campaign of 2007-2008</p> <p>Control group (n = 137): intramuscular injection of one 0.5 mL dose of placebo</p>	
Outcomes	<p>Primary outcomes: acute coronary syndrome (including myocardial infarction and unstable angina), coronary revascularisation, cardiovascular death</p> <p>Secondary outcomes: number of influenza episodes, physiological variables, adverse events</p> <p>Did the intervention group have significantly lower risk of influenza? Yes</p>	
Funding / conflict of interest	Funded by Shahid Beheshti Medical University, Tehran, Iran	
Notes		
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported; communication suggests that an inadequate method was used
Allocation concealment (selection bias)	High risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were blinded

IVCAD 2009 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Study author stated (personal communication) that outcome assessors were blinded to the interventions
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Losses to follow-up / non-completers	Low risk	Intervention group: 6/141 (4.3%) Control group: 6/137 (4.4%)
Intention-to-treat analysis	High risk	Not done
Selective reporting (reporting bias)	Unclear risk	Study authors stated that they reported all data
Similarity at baseline	Low risk	Study authors stated that groups were similar at baseline
Other bias	Unclear risk	No power analysis

Langley 2011a

Methods	<p>Setting: North America; multi-centre, no further details</p> <p>Design: individual randomisation, parallel-group, observer-blinded</p> <p>Dates and follow-up: trial dates January 28, 2008 to November 25, 2009; follow-up: study sites attended 42 days after dose 1; telephone interviews on day 84; 364 days for safety data</p>
Participants	<p>N: 4561 (2334/3422 completers in the intervention group and 770/1139 in the control group)</p> <p>Inclusion criteria: adults \geq 18 years; healthy or controlled chronic disease (no details given); not pregnant</p> <p>Age: <i>intervention:</i> 18 to 64 years (n = 2304): 38.5 years (range 18 to 64), \geq 65 years (n = 1118): 71.9 years (range 65 to 91); <i>control:</i> 18 to 64 years (n = 768): 38.7 years (range 18 to 64), \geq 65 years (n = 371): 72.1 years (range 65 to 89)</p> <p>Sex (% men): <i>intervention:</i> 18 to 64 years: 42.4%, \geq 65 years: 44.5%; <i>control:</i> 18 to 64 years: 44.8%, \geq 65 years: 47.2%</p> <p>Ethnicity: <i>intervention:</i> 18 to 64 years: 85.9% White European, 9.5% African heritage, \geq 65 years: 93.3% White European, 3.6% African heritage; <i>control:</i> 18 to 64 years: 84.2% White European, 11.9% African heritage, \geq 65 years: 93% White European, 3.8% African heritage</p> <p>Cardiovascular risk status: not reported</p>
Interventions	<p>Intervention (n = 3422): H5N1 vaccine antigen (GlaxoSmithKline); each dose contained 3.75 μg haemagglutinin antigen of A/Indonesia/05/2005; the adjuvant (AS03A) was a 10% (by volume) DL-alpha-tocopherol-based oil-in-water emulsion; vaccine recipients were randomised 1:1:1 to receive 1 of 3 lots of vaccine; participants received vaccine or placebo intramuscularly on day 0 and a second dose on day 21</p>

	Control (n = 1139): phosphate-buffered saline	
Outcomes	<p>Primary outcomes: immunogenicity and equivalence of 3 lots of vaccine</p> <p>Secondary outcomes: included safety analysis (including death from cardiovascular causes)</p> <p>Did the intervention group have significantly lower risk of influenza? Vaccine produced vaccine homologous haemagglutination inhibition antibodies that fulfilled licensure criteria for seroconversion and seroprotection in adults; unclear whether fewer people in the vaccine group actually had influenza infection</p>	
Funding / conflict of interest	GSK Biologicals, US Department of Health and Human Services	
Notes		
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation list was generated by GSK Biologicals using a blocking scheme; randomisation 3:1
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Vaccine was administered by unblinded staff, who took no further part in the study; vaccine and placebo injections were administered in overwrapped syringes to obscure contents to other study staff and participants
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Observer-blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Losses to follow-up / non-completers	Unclear risk	<p>Intervention group: 3422 vaccinated, 2606 agreed to day 364 follow-up, 272 dropouts (10.4% of 2606), including 42 lost to follow-up</p> <p>Control group: 1139 vaccinated, 870 agreed to day 364 follow-up, 100 dropouts (11.5% of 870), including 14 lost to follow-up</p>

Langley 2011a (Continued)

Intention-to-treat analysis	Low risk	Whole vaccinated cohort was included in the safety analysis - main outcome relevant for this review; no intention-to-treat analysis for vaccine effectiveness
Selective reporting (reporting bias)	Low risk	All outcomes were reported as specified
Similarity at baseline	Low risk	Groups were similar
Other bias	Low risk	Power analysis

Phrommintikul 2011

Methods	<p>Setting: Thailand; Department of Internal Medicine, no details stated</p> <p>Design: individual randomisation, parallel-group</p> <p>Dates and follow-up: recruitment November 2007 to October 2008; follow-up 12 months</p>
Participants	<p>N: 442 (220/221 completers in the intervention group and 217/218 in the control group)</p> <p>Inclusion criteria: patients > 50 years admitted with acute coronary syndrome within 8 weeks</p> <p>Age: <i>intervention:</i> 65 SD 9 years; <i>control:</i> 67 SD 9 years</p> <p>Sex (% men): <i>intervention:</i> 61%; <i>control:</i> 52%</p> <p>Ethnicity: not reported</p> <p>Cardiovascular risk status: <i>intervention:</i> 63.1% hypertension, 29.0% diabetes mellitus, 44.3% dyslipidaemia, 5.0% prior myocardial infarction; <i>control:</i> 61.6% hypertension, 32.1% diabetes mellitus, 49.5% dyslipidaemia, 4.2% prior myocardial infarction</p> <p>Type of acute coronary syndrome: <i>intervention:</i> 37% STEMI, 46% NSTEMI, 16% unstable angina; <i>control:</i> 35% STEMI, 48% NSTEMI, 17% unstable angina</p> <p>Pharmacological therapy: <i>intervention:</i> 97.7% aspirin, 76.0% β-blocker, 64.3% ACE inhibitor/angiotensin II receptor blocker, 86.9% statin <i>control:</i> 96.8% aspirin, 72.0% β-Blocker, 52.8% ACE inhibitor/angiotensin II receptor blocker (P value 0.02 between groups), 81.4% statin</p>
Interventions	<p>Intervention group (n = 221): single-dose intramuscular injection of 0.5 mL of split, inactivated influenza vaccine (no further details)</p> <p>Control group (n = 218): no intervention</p>
Outcomes	<p>Primary outcomes: cardiovascular outcomes (myocardial infarction, unstable angina, hospitalisation for acute coronary syndrome, heart failure or stroke, cardiovascular death)</p> <p>Secondary outcomes: not reported</p> <p>Did the intervention group have significantly lower risk of influenza? Not reported</p>
Funding / conflict of interest	Thailand Research Fund; no conflicts of interest
Notes	

<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated sequence in block randomisation size of 4
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Control was no treatment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Study nurses blinded to participants' treatment collected data; endpoints were verified by blinded cardiologists
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low attrition rate, ITT analysis was used
Losses to follow-up / non-completers	Low risk	Intervention group: 1/221 (0.45%) Control group: 1/218 (0.46%)
Intention-to-treat analysis	Low risk	ITT analysis done for all outcomes
Selective reporting (reporting bias)	Low risk	All outcomes reported as specified
Similarity at baseline	Unclear risk	Slight difference in baseline medication (ACE inhibitor/angiotensin II receptor blocker)
Other bias	Low risk	Power analysis (80% power to detect a difference in 1-year MACE incidence)

Wu 2010

Methods	Setting: China; setting not reported Design: individual randomisation, parallel-group, double-blind Dates and follow-up: trial dates July 22 to September 7, 2009; follow-up 42 days
Participants	N: 706 (601/606 completers in the intervention group and 100/100 in the control group) Inclusion criteria: healthy adults 18 to 60 years, no history of chronic disease (no more details reported) Age (mean, range): <i>intervention:</i> whole virion + Al 5 µg 41.3 SD 10.0 (18 to 60); whole virion + Al 10 µg 41.1 SD 9.9 (18 to 60); split virion + Al 7.5 µg 41.1 SD 10.2 (18 to 59); split virion + Al 15 µg 41.7 SD 10.1 (18 to 59); split virion 15 µg 41.6 SD 10.3 (18 to 60); split virion 30 µg: 41.9

	SD9.6 (19 to 60); <i>control</i> : 42.0 SD 9.8 (18 to 60) Sex (% men): <i>intervention</i> : 40%; <i>control</i> : 47% Ethnicity: not reported Cardiovascular risk status: not reported, no chronic disease	
Interventions	Intervention group (n = 606): vaccine strain X-179A, reassortant between A/California/07/2009 and A/PR/8/34 (Sinovac Biotech); 6 formulations of influenza A (H1N1) vaccine: 1. 5 µg whole virion with aluminium hydroxide (n = 101) 2. 10 µg whole virion vaccine with aluminium hydroxide (n = 102) 3. 7.5 µg split virion vaccine with aluminium hydroxide (n = 101) 4. 15 µg split virion vaccine with aluminium hydroxide (n = 100) 5. 15 µg split virion vaccine (n = 101) 6. 30 µg split virion vaccine (n = 101) The aluminium-adjutant formulation contained 0.3 to 0.6 mg/mL aluminium hydroxide; all formulas free of preservatives; 2 doses given, 21 days apart Control group (n = 100): phosphate buffer saline	
Outcomes	Primary outcomes: immunogenicity and safety Secondary outcomes: not reported Did the intervention group have significantly lower risk of influenza? Highest geometric mean titre ratio, seroprotection rate and seroconversion rate with 30 µg and 15 µg split virion vaccine; higher seroprotection rates associated with absence of aluminium adjuvant and higher dosage vaccine, no immune response with placebo	
Funding / conflict of interest	Support from US Centers for Disease Control and Prevention and UK National Institute for Biological Standards and Control (provided vaccine strands and standards); study authors included people working for Sinovac Biotech	
Notes		
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation list was generated by statistician not involved in the rest of the trial using SAS software
Allocation concealment (selection bias)	Low risk	s.o.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Vaccinators, investigators and participants were blinded to treatment assignment for the duration of the study; all eligible participants were given a randomised subject number and were vaccinated according to the numbers on the vaccine labels, which were the same as the randomised participant numbers

Blinding of outcome assessment (detection bias) All outcomes	Low risk	s.o.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low attrition rate, ITT analysis
Losses to follow-up / non-completers	Low risk	Intervention group Whole virion + Al 5 µg 3/101 (3%) Whole virion + Al 10 µg 1/102 (1%) Split virion + Al 7.5 µg 1/101 (1%) Split virion + Al 15 µg 0 Split virion 15 µg 0 Split virion 30 µg 0 Control group: 0
Intention-to-treat analysis	Low risk	Done for immunogenicity and safety
Selective reporting (reporting bias)	Low risk	All outcomes were reported as specified
Similarity at baseline	Low risk	Groups were similar
Other bias	Unclear risk	Limited baseline characteristics, with power analysis not reported

ACE: angiotensin-converting enzyme.

ITT: intention-to-treat.

MACE: composite of cardiovascular death, acute MI, coronary revascularization.

MI: myocardial infarction.

NSTEMI: non-ST segment elevation myocardial infarction.

PCI: percutaneous cardiac intervention.

SD: standard deviation.

STEMI: ST segment elevation myocardial infarction.

WHO: World Health Organisation.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Allsup 2004	No eligible outcomes
Baluch 2012	No placebo/no intervention control
Blumberg 1998	No eligible outcomes

(Continued)

Brydak 2009	No eligible outcomes, part of FLUCAD
Christenson 2008	Not an RCT
De Bernardi 2002	Not a placebo-controlled study
DiazGranados 2013	No placebo/no intervention control
Falchetti 2000	No available data on any of the outcomes
Falsey 2008	No placebo/no intervention control, no eligible outcomes
Farrow 1984	No available data on any of the outcomes
Fletcher 1997	No placebo/no intervention control
Garcia 2009	Not an RCT
Grau 2005	Not an RCT
Gurfinkel 2002	Not an RCT, refers to FLUVACS study
Honkanen 2006	Not an RCT
Hui 2006a	No available data on any of the outcomes
Hui 2006b	No eligible outcomes
Iorio 2010	No eligible outcomes
Jackson 1999	No available data on any of the outcomes
Kalyagin 2012	Not an RCT
Langley 2011b	No eligible outcomes
Li 2008	No placebo/no intervention control
Ljungman 2005	Not a placebo-controlled study
MacIntyre 2007	Trial withdrawn and replaced by case-control study
Madjid 2004	Not an RCT
Magnani 2005a	No available data on any of the outcomes
Magnani 2005b	No eligible outcomes

(Continued)

McElhanev 2013	No placebo/no intervention control
McNeil 2007	No placebo/no intervention control
Morales 2003	No placebo/no intervention control
Musto 1997	No available data on any of the outcomes
Nichol 1999	No available data on any of the outcomes
Ohmit 2006	No eligible outcomes
Plasai 2006	Not an RCT
Reisinger 2009	No placebo/no intervention control
Scheifele 2003	No eligible outcomes
Scheifele 2013	No eligible outcomes
Schwarz 2011	No placebo/no intervention control
Sinnecker 1987	No available data on any of the outcomes
Vardeny 2011	No placebo/no intervention control
Zhu 2009	No eligible outcomes
Zimmermann 2013	No placebo/no intervention control

Characteristics of ongoing studies [ordered by study ID]

NCT01945268

Trial name or title	Title: Influenza vaccine to prevent adverse vascular events: a pilot study
Methods	Design: RCT, double-blind
Participants	Target N: 600 Inclusion criteria: age \geq 18 years and New York Heart Association functional class II, III and IV
Interventions	Intervention: 0.5 mL of inactivated trivalent influenza vaccine recommended for the influenza season 2013-2014 Control: 0.5 mL of sterile saline
Outcomes	Major adverse vascular events; economic evaluation

NCT01945268 (Continued)

Starting date	October 2014
Contact information	Loeb M, McMaster University, loebm@mcmaster.ca
Notes	

DATA AND ANALYSES

Comparison 1. Vaccine versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 Safety analysis studies including cardiovascular outcomes	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Cardiovascular death	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Secondary prevention studies	4	1667	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.26, 0.76]
2.2 Secondary prevention studies - participants with stable angina/PCI	2	602	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.07, 1.73]
2.3 Secondary prevention studies - participants with acute coronary symptoms/MI	2	350	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.04, 5.20]
2.4 Safety analysis studies including cardiovascular outcomes	2	6399	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.06, 7.62]
3 Major adverse coronary events (MACE)	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 All	2		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 Participants with acute coronary symptoms	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.3 Participants with stable angina	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4 Coronary ischaemic event (MACE or hospitalisation for myocardial ischaemia)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.1 All	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.2 Participants with acute coronary symptoms	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.3 Participants with stable angina	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5 Double endpoint (CV death, non-fatal MI or severe recurrent ischaemia)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5.1 All	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5.2 Myocardial infarction	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6 Triple endpoint (CV death, non-fatal MI or severe recurrent ischaemia)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6.1 All	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6.2 Myocardial infarction	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6.3 PCI	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

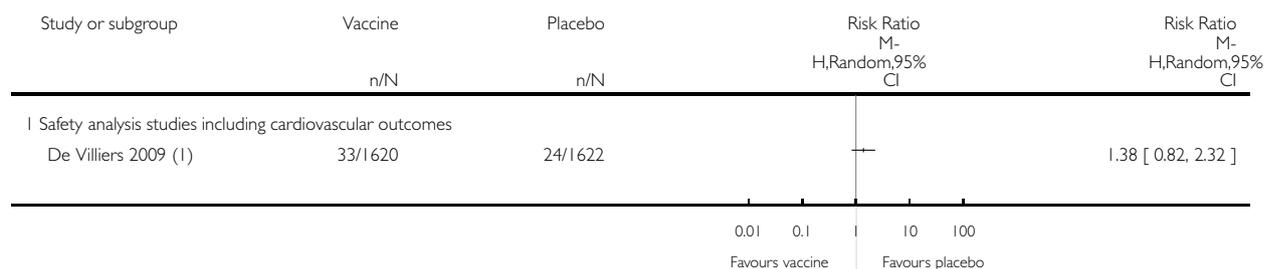
7 At least 1 cardiovascular event	1	Risk Ratio (M-H, Random, 95% CI)	Totals not selected
8 Coronary artery bypass graft (CABG)	1	Risk Ratio (M-H, Random, 95% CI)	Totals not selected
9 Percutaneous coronary intervention (PCI)	1	Risk Ratio (M-H, Random, 95% CI)	Totals not selected
10 Myocardial infarction	3	Risk Ratio (M-H, Random, 95% CI)	Totals not selected
10.1 All	2	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
10.2 Participants with acute coronary symptoms/MI	2	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
10.3 Participants with stable angina/PCI	2	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
11 Stroke/hospitalisation for acute stroke	1	Risk Ratio (M-H, Random, 95% CI)	Totals not selected
12 Hospitalisation for heart failure	1	Risk Ratio (M-H, Random, 95% CI)	Totals not selected
13 Angina/unstable angina	1	Risk Ratio (M-H, Random, 95% CI)	Totals not selected
14 Hospitalisation for acute coronary syndrome/myocardial ischaemia	3	Risk Ratio (M-H, Random, 95% CI)	Totals not selected
14.1 All	2	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.2 Participants with acute coronary symptoms	2	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.3 Participants with stable angina	1	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15 Coronary revascularisation (PCI/CABG)	2	Risk Ratio (M-H, Random, 95% CI)	Totals not selected
15.1 All	1	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15.2 Participants with acute coronary symptoms	1	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15.3 Participants with stable angina	2	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 Vaccine versus placebo, Outcome 1 All-cause mortality.

Review: Influenza vaccines for preventing cardiovascular disease

Comparison: 1 Vaccine versus placebo

Outcome: 1 All-cause mortality



or cerebrovascular disorders, and that these occurred in statistically similar proportions of vaccine and placebo recipients (all $p \geq 0.422$)

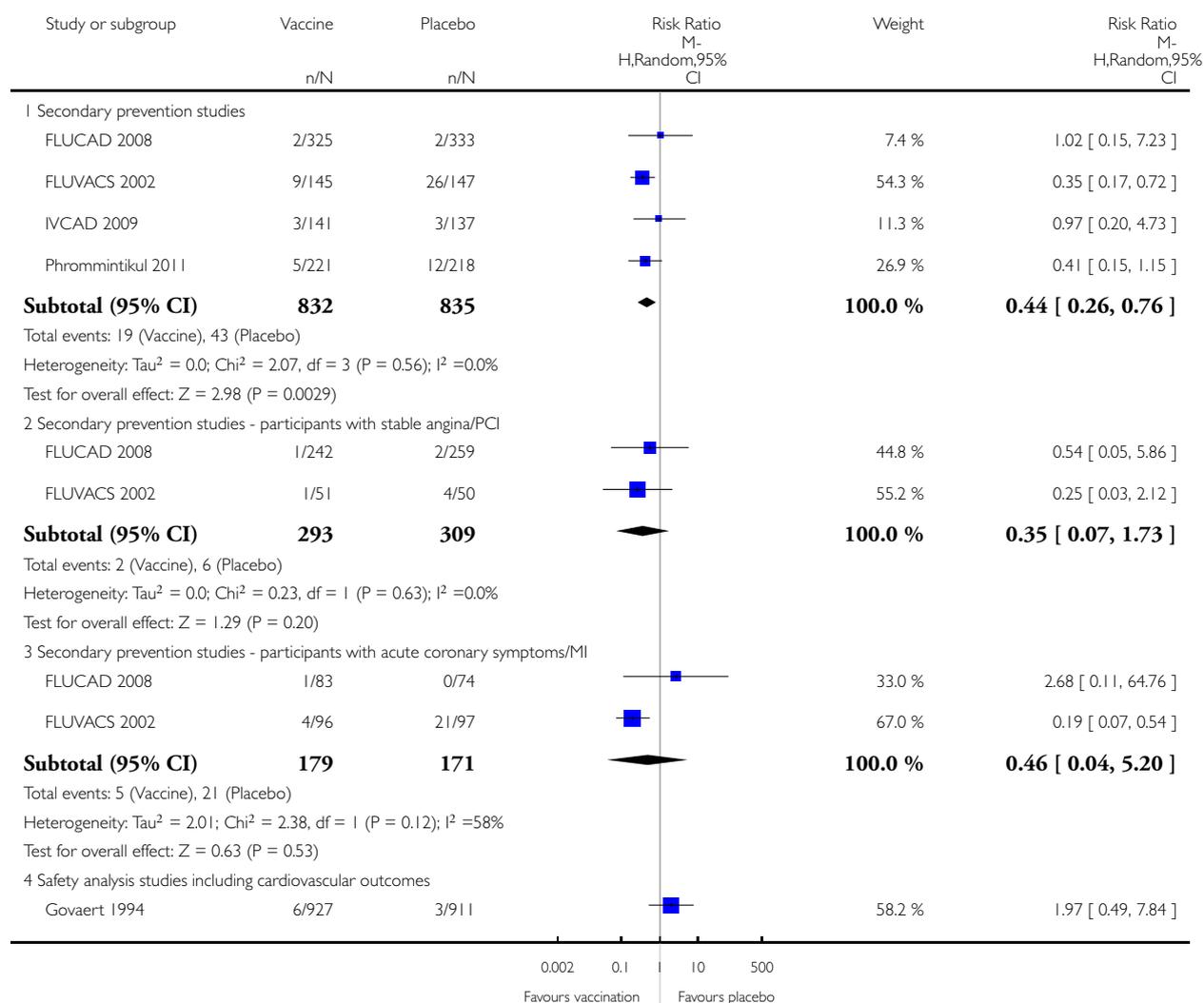
(1) This is for death by all causes; distribution of causes of death not given for the groups but stated that the most frequent causes of death were myocardial infarction, cardiac failure,

Analysis 1.2. Comparison 1 Vaccine versus placebo, Outcome 2 Cardiovascular death.

Review: Influenza vaccines for preventing cardiovascular disease

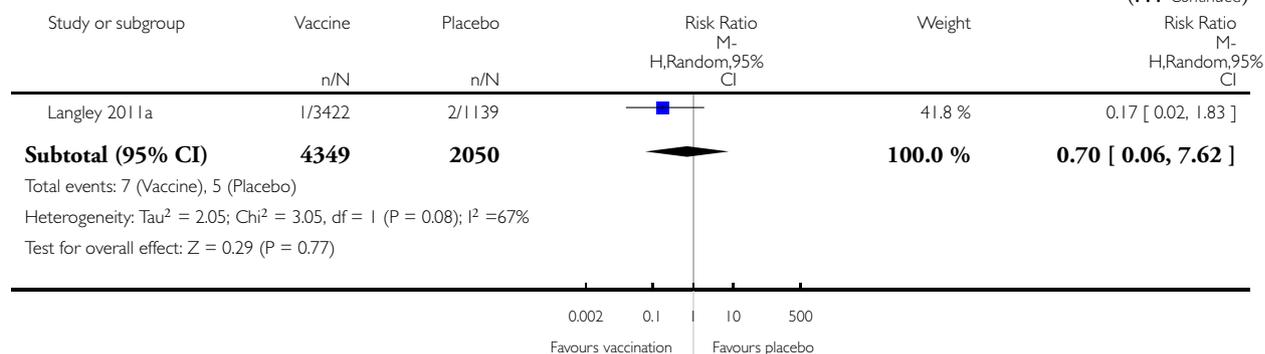
Comparison: 1 Vaccine versus placebo

Outcome: 2 Cardiovascular death



(Continued ...)

(... Continued)

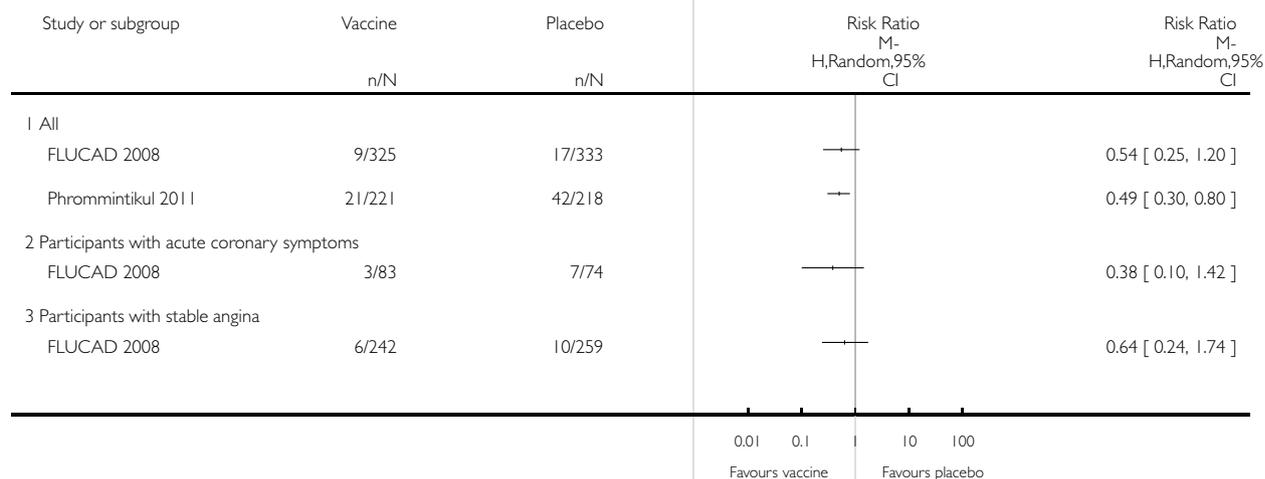


Analysis 1.3. Comparison 1 Vaccine versus placebo, Outcome 3 Major adverse coronary events (MACE).

Review: Influenza vaccines for preventing cardiovascular disease

Comparison: 1 Vaccine versus placebo

Outcome: 3 Major adverse coronary events (MACE)

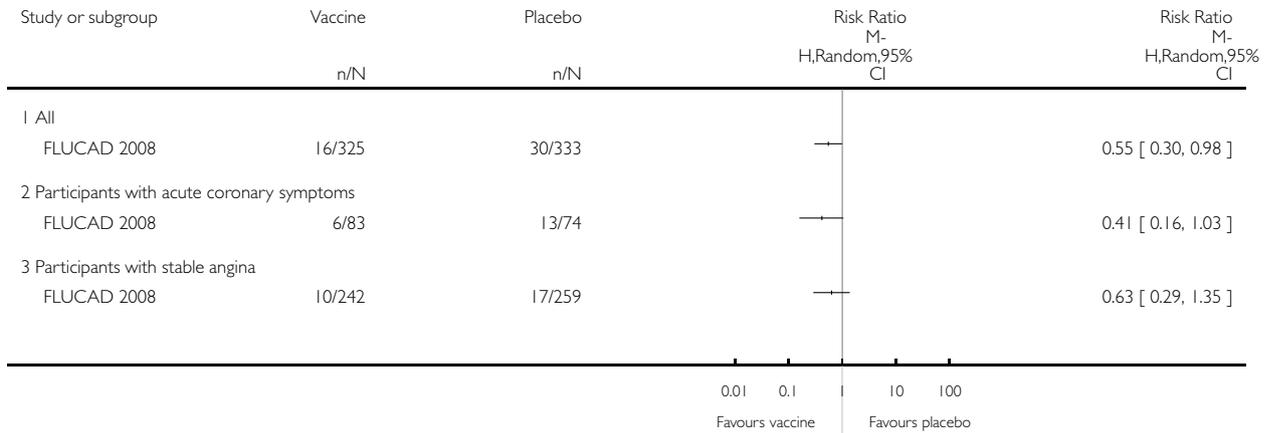


Analysis 1.4. Comparison 1 Vaccine versus placebo, Outcome 4 Coronary ischaemic event (MACE or hospitalisation for myocardial ischaemia).

Review: Influenza vaccines for preventing cardiovascular disease

Comparison: 1 Vaccine versus placebo

Outcome: 4 Coronary ischaemic event (MACE or hospitalisation for myocardial ischaemia)

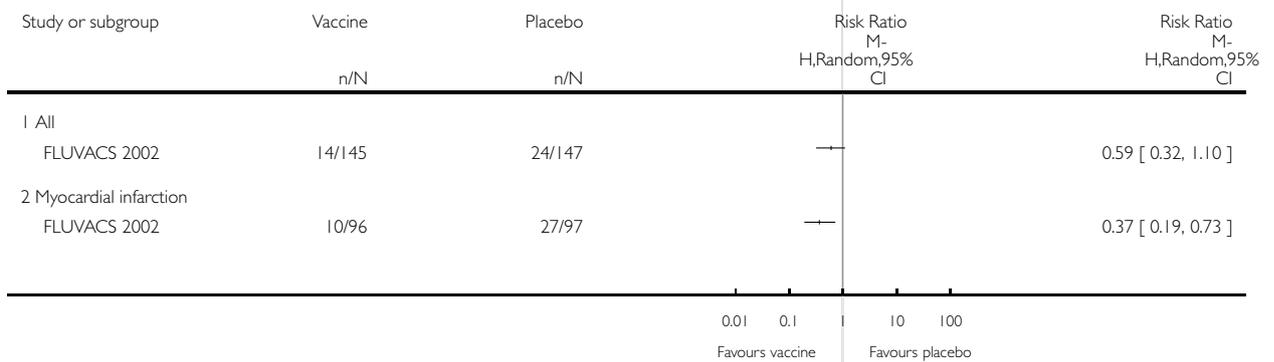


Analysis 1.5. Comparison 1 Vaccine versus placebo, Outcome 5 Double endpoint (CV death, non-fatal MI or severe recurrent ischaemia).

Review: Influenza vaccines for preventing cardiovascular disease

Comparison: 1 Vaccine versus placebo

Outcome: 5 Double endpoint (CV death, non-fatal MI or severe recurrent ischaemia)

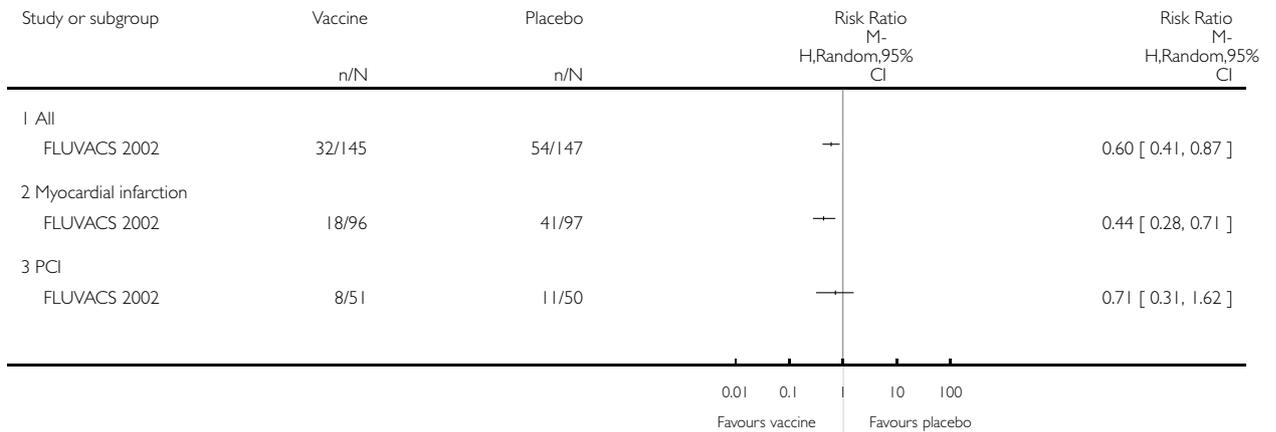


Analysis 1.6. Comparison 1 Vaccine versus placebo, Outcome 6 Triple endpoint (CV death, non-fatal MI or severe recurrent ischaemia).

Review: Influenza vaccines for preventing cardiovascular disease

Comparison: 1 Vaccine versus placebo

Outcome: 6 Triple endpoint (CV death, non-fatal MI or severe recurrent ischaemia)

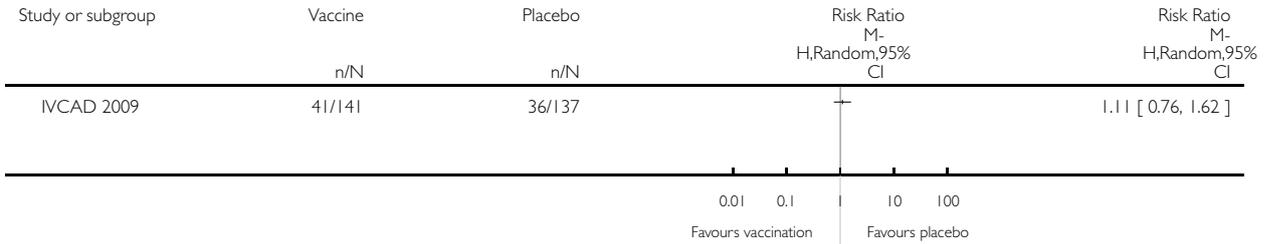


Analysis I.7. Comparison I Vaccine versus placebo, Outcome 7 At least 1 cardiovascular event.

Review: Influenza vaccines for preventing cardiovascular disease

Comparison: I Vaccine versus placebo

Outcome: 7 At least 1 cardiovascular event

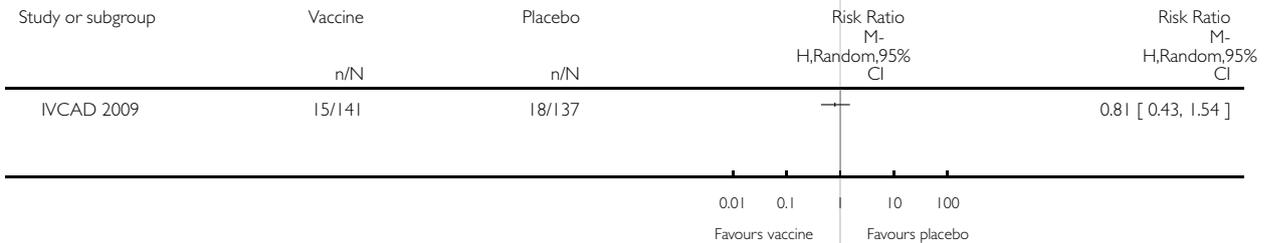


Analysis I.8. Comparison I Vaccine versus placebo, Outcome 8 Coronary artery bypass graft (CABG).

Review: Influenza vaccines for preventing cardiovascular disease

Comparison: I Vaccine versus placebo

Outcome: 8 Coronary artery bypass graft (CABG)

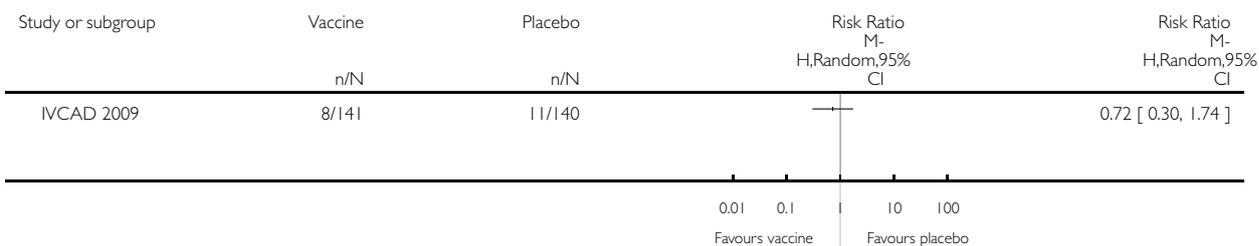


Analysis 1.9. Comparison 1 Vaccine versus placebo, Outcome 9 Percutaneous coronary intervention (PCI).

Review: Influenza vaccines for preventing cardiovascular disease

Comparison: 1 Vaccine versus placebo

Outcome: 9 Percutaneous coronary intervention (PCI)

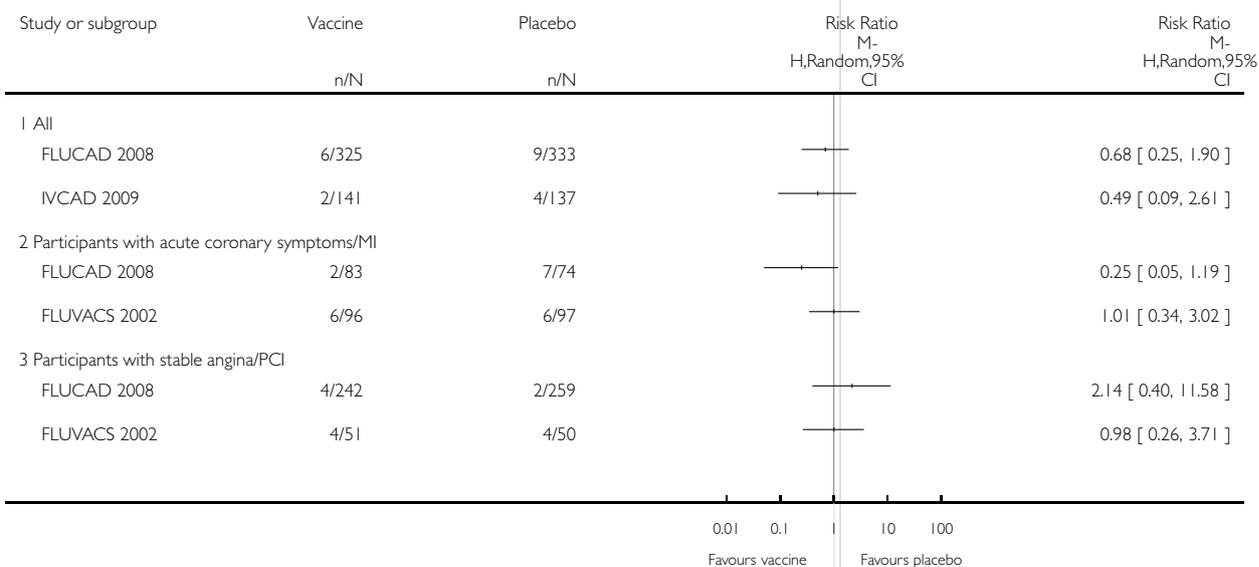


Analysis 1.10. Comparison 1 Vaccine versus placebo, Outcome 10 Myocardial infarction.

Review: Influenza vaccines for preventing cardiovascular disease

Comparison: 1 Vaccine versus placebo

Outcome: 10 Myocardial infarction

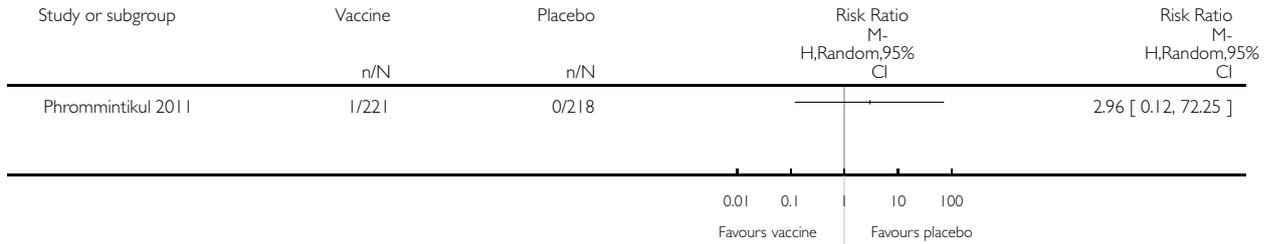


Analysis 1.11. Comparison 1 Vaccine versus placebo, Outcome 11 Stroke/hospitalisation for acute stroke.

Review: Influenza vaccines for preventing cardiovascular disease

Comparison: 1 Vaccine versus placebo

Outcome: 11 Stroke/hospitalisation for acute stroke

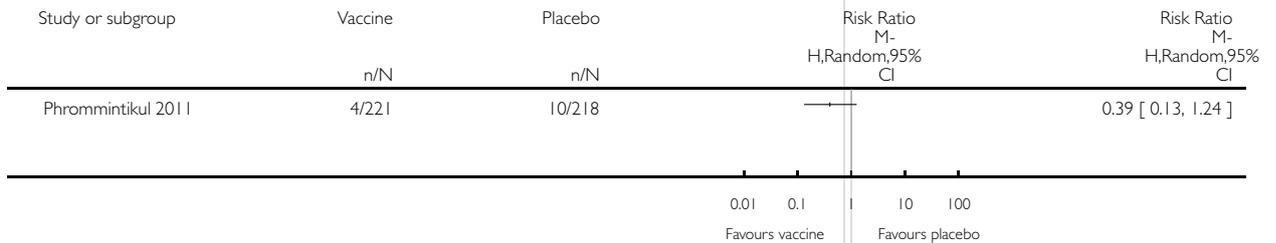


Analysis 1.12. Comparison 1 Vaccine versus placebo, Outcome 12 Hospitalisation for heart failure.

Review: Influenza vaccines for preventing cardiovascular disease

Comparison: 1 Vaccine versus placebo

Outcome: 12 Hospitalisation for heart failure

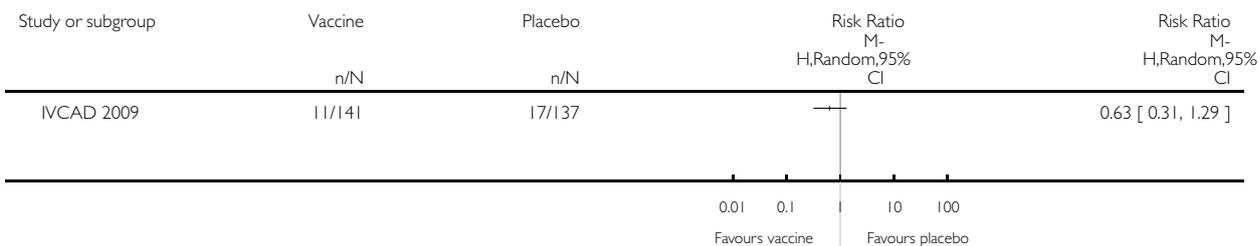


Analysis 1.13. Comparison 1 Vaccine versus placebo, Outcome 13 Angina/unstable angina.

Review: Influenza vaccines for preventing cardiovascular disease

Comparison: 1 Vaccine versus placebo

Outcome: 13 Angina/unstable angina

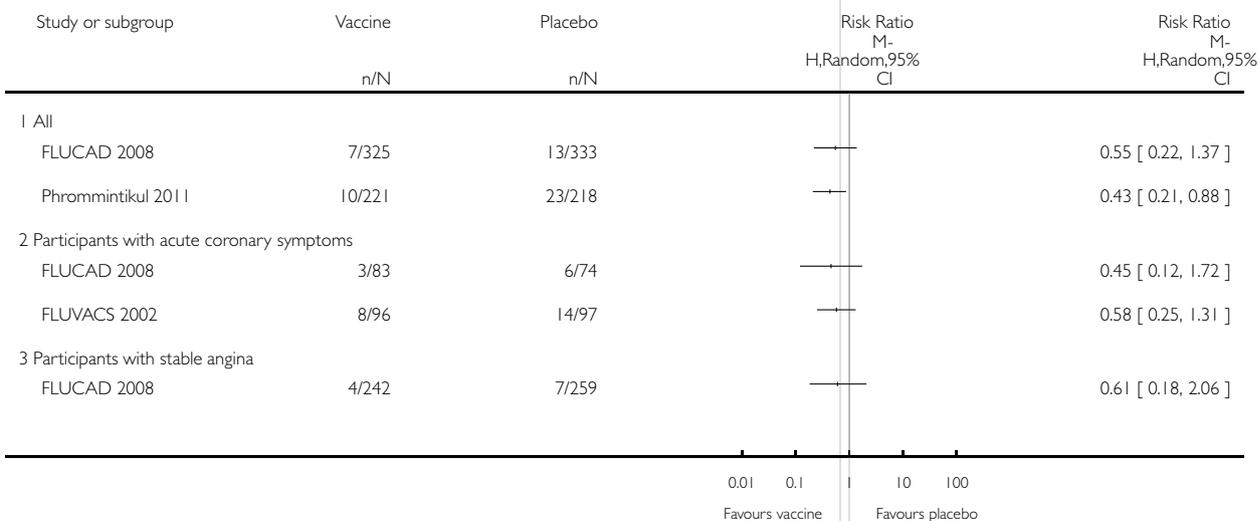


Analysis 1.14. Comparison 1 Vaccine versus placebo, Outcome 14 Hospitalisation for acute coronary syndrome/myocardial ischaemia.

Review: Influenza vaccines for preventing cardiovascular disease

Comparison: 1 Vaccine versus placebo

Outcome: 14 Hospitalisation for acute coronary syndrome/myocardial ischaemia

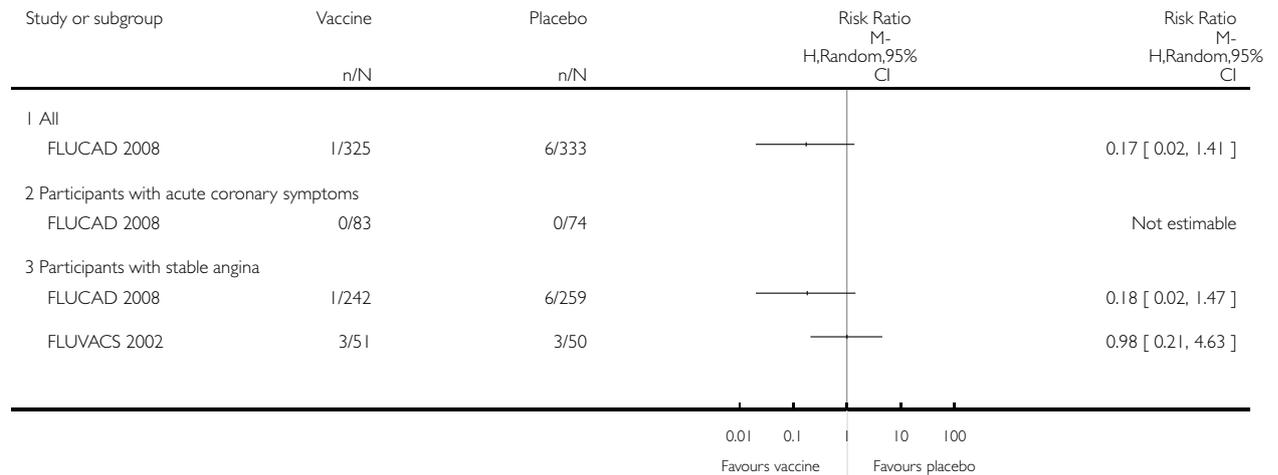


Analysis 1.15. Comparison 1 Vaccine versus placebo, Outcome 15 Coronary revascularisation (PCI/CABG).

Review: Influenza vaccines for preventing cardiovascular disease

Comparison: 1 Vaccine versus placebo

Outcome: 15 Coronary revascularisation (PCI/CABG)



APPENDICES

Appendix 1. Search strategies 2013 - cardiovascular disease

The Cochrane Library

#1MeSH descriptor: [Influenza Vaccines] this term only

#2(influenza* near vaccin*)

#3(influenza* near immuni*)

#4(flu near immuni*)

#5(flu near vaccin*)

#6(#1 or #2 or #3 or #4 or #5)

#7MeSH descriptor: [Cardiovascular Diseases] explode all trees

#8cardio*

#9cardia*

#10heart*

#11coronary*

#12angina*

#13ventric*

#14myocard*

#15pericard*
 #16isch?em*
 #17emboli*
 #18arrhythmi*
 #19thrombo*
 #20atrial next fibrillat*
 #21tachycardi*
 #22endocardi*
 #23(sick next sinus)
 #24MeSH descriptor: [Stroke] explode all trees
 #25(stroke or strokes)
 #26cerebrovasc*
 #27cerebral next vascular
 #28apoplexy
 #29(brain near/2 accident*)
 #30((brain* or cerebral or lacunar) near/2 infarct*)
 #31MeSH descriptor: [Hypertension] explode all trees
 #32hypertensi*
 #33(peripheral next arter* next disease*)
 #34((high or increased or elevated) near/2 blood pressure)
 #35MeSH descriptor: [Hyperlipidemias] explode all trees
 #36hyperlipid*
 #37hyperlip?emia*
 #38hypercholesterol*
 #39hypercholester?emia*
 #40hyperlipoprotein?emia*
 #41hypertriglycerid?emia*
 #42MeSH descriptor: [Arteriosclerosis] explode all trees
 #43MeSH descriptor: [Cholesterol] explode all trees
 #44cholesterol
 #45“coronary risk factor*”
 #46MeSH descriptor: [Blood Pressure] this term only
 #47“blood pressure”
 #48#7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47
 #49#6 and #48

MEDLINE Ovid

1. Influenza Vaccines/
2. (influenza\$ adj3 immuni\$).tw.
3. (flu adj3 vaccin\$).tw.
4. (flu adj3 immuni\$).tw.
5. (influenza adj3 vaccin\$).tw.
6. flumist.tw.
7. (laiv adj2 vaccin*).tw.
8. (caiv-t adj2 vaccin*).tw.
9. or/1-8
10. exp Cardiovascular Diseases/
11. cardio*.tw.
12. cardia*.tw.
13. heart*.tw.

14. coronary*.tw.
15. angina*.tw.
16. ventric*.tw.
17. myocard*.tw.
18. pericard*.tw.
19. isch?em*.tw.
20. emboli*.tw.
21. arrhythmi*.tw.
22. thrombo*.tw.
23. atrial fibrillat*.tw.
24. tachycardi*.tw.
25. endocardi*.tw.
26. (sick adj sinus).tw.
27. exp Stroke/
28. (stroke or stokes).tw.
29. cerebrovasc*.tw.
30. cerebral vascular.tw.
31. apoplexy.tw.
32. (brain adj2 accident*).tw.
33. ((brain* or cerebral or lacunar) adj2 infarct*).tw.
34. exp Hypertension/
35. hypertensi*.tw.
36. peripheral arter* disease*.tw.
37. ((high or increased or elevated) adj2 blood pressure).tw.
38. exp Hyperlipidemias/
39. hyperlipid*.tw.
40. hyperlip?emia*.tw.
41. hypercholesterol*.tw.
42. hypercholester?emia*.tw.
43. hyperlipoprotein?emia*.tw.
44. hypertriglycerid?emia*.tw.
45. exp Arteriosclerosis/
46. exp Cholesterol/
47. cholesterol.tw.
48. "coronary risk factor* ".tw.
49. Blood Pressure/
50. blood pressure.tw.
51. or/10-50
52. 9 and 51
53. randomized controlled trial.pt.
54. controlled clinical trial.pt.
55. randomized.ab.
56. placebo.ab.
57. drug therapy.fs.
58. randomly.ab.
59. trial.ab.
60. groups.ab.
61. 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60
62. exp animals/ not humans.sh.
63. 61 not 62
64. 52 and 63

EMBASE Ovid

1. influenza vaccine/
2. (influenza\$ adj3 immuni\$).tw.
3. (flu adj3 vaccin\$).tw.
4. (flu adj3 immuni\$).tw.
5. (influenza adj3 vaccin\$).tw.
6. flumist.tw.
7. (laiv adj2 vaccin*).tw.
8. (caiv-t adj2 vaccin*).tw.
9. or/1-8
10. exp cardiovascular disease/
11. cardio*.tw.
12. cardia*.tw.
13. heart*.tw.
14. coronary*.tw.
15. angina*.tw.
16. ventric*.tw.
17. myocard*.tw.
18. pericard*.tw.
19. isch?em*.tw.
20. emboli*.tw.
21. arrhythmi*.tw.
22. thrombo*.tw.
23. atrial fibrillat*.tw.
24. tachycardi*.tw.
25. endocardi*.tw.
26. (sick adj sinus).tw.
27. exp cerebrovascular disease/
28. (stroke or stokes).tw.
29. cerebrovasc*.tw.
30. cerebral vascular.tw.
31. apoplexy.tw.
32. (brain adj2 accident*).tw.
33. ((brain* or cerebral or lacunar) adj2 infarct*).tw.
34. exp hypertension/
35. hypertensi*.tw.
36. peripheral arter* disease*.tw.
37. ((high or increased or elevated) adj2 blood pressure).tw.
38. exp hyperlipidemia/
39. hyperlipid*.tw.
40. hyperlip?emia*.tw.
41. hypercholesterol*.tw.
42. hypercholester?emia*.tw.
43. hyperlipoprotein?emia*.tw.
44. hypertriglycerid?emia*.tw.
45. exp Arteriosclerosis/
46. exp Cholesterol/
47. cholesterol.tw.
48. "coronary risk factor*".tw.
49. Blood Pressure/
50. blood pressure.tw.
51. or/10-50

52. 9 and 51
53. random\$.tw.
54. factorial\$.tw.
55. crossover\$.tw.
56. cross over\$.tw.
57. cross-over\$.tw.
58. placebo\$.tw.
59. (doubl\$ adj blind\$).tw.
60. (singl\$ adj blind\$).tw.
61. assign\$.tw.
62. allocat\$.tw.
63. volunteer\$.tw.
64. crossover procedure/
65. double blind procedure/
66. randomized controlled trial/
67. single blind procedure/
68. 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67
69. (animal/ or nonhuman/) not human/
70. 68 not 69
71. 52 and 70

Web of Science

- #12 #11 AND #10
 #11 TS=(random* or blind* or allocat* or assign* or trial* or placebo* or crossover* or cross-over*)
 #10 #9 AND #1
 #9 #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2
 #8 TS=(hyperlipid* OR hyperlip?emia* OR hypercholesterol* OR hypercholester?emia* OR hyperlipoprotein?emia* OR hypertriglycerid?emia*)
 #7 TS=("high blood pressure")
 #6 TS=(hypertensi* OR "peripheral arter* disease*")
 #5 TS=(stroke OR stokes OR cerebrovasc* OR cerebral OR apoplexy OR (brain SAME accident*) OR (brain SAME infarct*))
 #4 TS=("atrial fibrillat*" OR tachycardi* OR endocardi*)
 #3 TS=(pericard* OR isch?em* OR emboli* OR arrhythmi* OR thrombo*)
 #2 TS=(cardio* OR cardia* OR heart* OR coronary* OR angina* OR ventric* OR myocard*)
 #1 TS=((influenza* OR flu OR laiv OR caiv-t) NEAR/3 (immuni* OR vaccin*)) OR flumist)

Limited PubMed search 20 February 2015

((vaccine* OR vaccinat*) AND (influenza OR flu) AND (cardiovascular OR heart OR coronary OR stroke)) in PubMed Clinical Queries

Similar (adapted) search in www.controlled-trials.com and www.clinicaltrials.gov

Appendix 2. Search strategies 2008 - coronary heart disease

CENTRAL (2007, Issue 4)

- #1 INFLUENZA VACCINE
- #2 (influenza* near vaccin*)
- #3 (influenza* near immuni*)
- #4 (flu near immuni*)
- #5 (flu near vaccin*)
- #6 (#1 or #2 or #3 or #4 or #5)
- #7 CARDIOVASCULAR DISEASES
- #8 heart
- #9 coronary
- #10 cardiac
- #11 myocardial
- #12 cardiovascular
- #13 angina
- #14 (#7 or #8 or #9 or #10 or #11 or #12 or #13)
- #15 (#6 and #14)

MEDLINE (to January 2008)

- 1 Influenza Vaccine/
- 2 (influenza\$ adj3 immuni\$).tw.
- 3 (flu adj3 vaccin\$).tw.
- 4 (flu adj3 immuni\$).tw.
- 5 (influenza adj3 vaccin\$).tw.
- 6 or/1-5
- 7 exp cardiovascular diseases/
- 8 myocardial.tw.
- 9 angina.tw.
- 10 coronary.tw.
- 11 heart.tw.
- 12 cardiac.tw.
- 13 cardiovascular.tw
- 14 or/7-13
- 15 6 and 14
- 16 randomized controlled trial.pt.
- 17 controlled clinical trial.pt.
- 18 Randomized controlled trials/
- 19 random allocation/
- 20 double blind method/
- 21 single-blind method/
- 22 or/16-21
- 23 exp animal/ not humans/
- 24 22 not 23
- 25 clinical trial.pt.
- 26 exp Clinical trials/
- 27 (clin\$ adj25 trial\$).ti,ab.
- 28 ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj (blind\$ or mask\$)).ti,ab.
- 29 placebos/
- 30 placebo\$.ti,ab.
- 31 random\$.ti,ab.

32 research design/
33 or/25-32
34 33 not 23
35 34 not 24
36 comparative study.pt.
37 exp evaluation studies/
38 follow up studies/
39 prospective studies/
40 (control\$ or prospectiv\$ or volunteer\$).ti,ab.
41 or/36-40
42 41 not 23
43 42 not (24 or 35)
44 24 or 35 or 43
45 15 and 44
46 limit 45 to yr="2005 - 2008"

EMBASE (to January 2008)

1 Influenza Vaccine/
2 (influenza\$ adj3 immuni\$).tw.
3 (flu adj3 vaccin\$).tw.
4 (flu adj3 immuni\$).tw.
5 (influenza adj3 vaccin\$).tw.
6 or/1-5
7 exp cardiovascular disease/
8 myocardial.tw.
9 angina.tw.
10 coronary.tw.
11 heart.tw.
12 cardiac.tw.
13 cardiovascular.tw.
14 or/7-13
15 6 and 14
16 clinical trial/
17 random\$.tw.
18 randomized controlled trial/
19 trial\$.tw.
20 follow-up.tw.
21 double blind procedure/
22 placebo\$.tw.
23 placebo/
24 factorial\$.ti,ab.
25 (crossover\$ or cross-over\$).ti,ab.
26 (double\$ adj blind\$).ti,ab.
27 (singl\$ adj blind\$).ti,ab.
28 assign\$.ti,ab.
29 allocat\$.ti,ab.
30 volunteer\$.ti,ab.
31 Crossover Procedure/
32 Single Blind Procedure/
33 or/16-32
34 15 and 33
35 limit 34 to yr="2005 - 2008"

WHAT'S NEW

Last assessed as up-to-date: 18 October 2013.

Date	Event	Description
17 February 2015	New citation required and conclusions have changed	Six studies were added to the two included in the previous version of this review. With the additional studies, evidence suggests that in patients with cardiovascular disease, influenza vaccination may reduce cardiovascular mortality and combined cardiovascular events
2 December 2014	New search has been performed	This review has been updated since its first publication in 2008. The scope has been increased to cover all cardiovascular disease (primary and secondary prevention), not just coronary heart disease. A new review author team took on the update of this review

HISTORY

Protocol first published: Issue 4, 2004

Review first published: Issue 3, 2008

Date	Event	Description
13 April 2008	Amended	Converted to new review format

CONTRIBUTIONS OF AUTHORS

Christine Clar: study selection, data extraction and quality assessment, data analysis and development of tables, figures and review text.

Zainab Oseni: data extraction and quality assessment.

Nadine Flowers: study selection.

Maryam Keshtkar-Jahromi: advice on new references for introduction and revisions of review draft.

Karen Rees: advice on study selection, reviewing of review text and supervision of ZO and NF.

DECLARATIONS OF INTEREST

None known.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The following changes in inclusion criteria and review methodology were made in the 2015 update of the review.

- Inclusion criteria: prevention of cardiovascular disease, not just coronary heart disease.
- Analysis: use of random-effects model instead of fixed-effect model.

INDEX TERMS

Medical Subject Headings (MeSH)

Coronary Disease [mortality; *prevention & control]; Influenza Vaccines [*therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Humans