

Supplementary Online Content

Udell JA, Zawi R, Bhatt DL, Keshtkar-Jahromi M, Gaughran F, Phrommintikul A, et al. Association between influenza vaccination and cardiovascular outcomes in high-risk patients: a meta-analysis. *JAMA*. doi: 10.1001/jama.2013.279206

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eReferences

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods: Search Strategies for MEDLINE and EMBASE

Database: Ovid MEDLINE(R) <1946 to August Week 3 2013>

Search Strategy:

- 1 chronic disease\$.mp. or exp chronic disease/ (246231)
- 2 risk.mp. (1489984)
- 3 exp mortality/ or mortality.mp. or exp death/ or death.mp. (1062095)
- 4 comorbidit\$.mp. or exp comorbidity/ or multimorbidit\$.mp. (68371)
- 5 (cardiovascular or cardiac or myocardial or heart or coronary).mp. (1571930)
- 6 (cardiovascular mortality or cardiovascular risk).mp. (44280)
- 7 exp vaccination/ or vaccination.mp. or vaccine\$.mp. or exp vaccines/ or shot\$.mp. or inoculation\$.mp. or injection\$.mp. (864179)
- 8 influenza\$.mp. or exp influenza/ or flu.mp. (101460)
- 9 influenza vaccine\$.mp. or exp influenza vaccines/ or flu vaccine\$.mp. or flu vaccination\$.mp. or influenza vaccination\$.mp. or flu shot\$.mp. or influenza shot\$.mp. or flu injection\$.mp. or flu inoculation\$.mp. or influenza injection\$.mp. or influenza inoculation\$.mp. (18939)
- 10 1 or 2 or 3 or 4 (2524432)
- 11 5 or 6 (1571930)
- 12 7 or 8 or 9 (934632)
- 13 10 and 11 and 12 (8964)
- 14 limit 13 to randomized controlled trial (740)
- 15 7 and 8 and 9 (18883)
- 16 15 and 10 (4987)
- 17 limit 16 to randomized controlled trial (220)
- 18 14 or 17 (945)

Database: Embase Classic+Embase <1947 to 2013 Week 35>

Search Strategy:

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- 2 risk.mp. (2116404)
- 3 exp mortality/ or mortality.mp. or exp death/ or death.mp. (1629524)
- 4 comorbidit\$.mp. or exp comorbidity/ or multimorbidit\$.mp. (117570)
- 5 (cardiovascular or cardiac or myocardial or heart or coronary).mp. (2456517)
- 6 exp cardiovascular mortality/ or cardiovascular mortality.mp. or cardiovascular risk/ or cardiovascular risk.mp. (136409)
- 7 exp vaccination/ or vaccination.mp. or vaccine\$.mp. or exp vaccine/ or shot\$.mp. or inoculation\$.mp. or injection\$.mp. (1091439)
- 8 influenza\$.mp. or exp influenza/ or flu.mp. (160564)
- 9 influenza vaccine\$.mp. or exp influenza vaccine/ or flu vaccine\$.mp. or exp influenza vaccination/ or flu vaccination\$.mp. or influenza vaccination\$.mp. or flu shot\$.mp. or influenza shot\$.mp. or flu injection\$.mp. or flu inoculation\$.mp. or influenza injection\$.mp. or influenza inoculation\$.mp. (31363)
- 10 1 or 2 or 3 or 4 (3539427)
- 11 5 or 6 (2456517)
- 12 7 or 8 or 9 (1198351)
- 13 10 and 11 and 12 (17639)
- 14 limit 13 to randomized controlled trial (968)
- 15 7 and 8 and 9 (31330)
- 16 15 and 10 (10425)
- 17 limit 16 to randomized controlled trial (290)
- 18 14 or 17 (1218)

eMethods: Data Extraction

The following study characteristics were systematically extracted: publication year, study initiation year, study duration, study location, sample size, baseline patient characteristics, mean age, proportion of women, type of influenza vaccine studied, type of control therapy, and number/type of cardiovascular outcomes or safety events. We included results only once from repeated publications of the same trial population. We referred to an original publication when an eligible article referred to a prior description of the study design. The principal investigators of eligible published trials were contacted to request additional details of follow-up duration and outcomes when available and not reported in an original or secondary publication. We included trials with absolute numbers of a first-occurrence composite endpoint, or fatal or non-fatal cardiovascular events, recorded by treatment arm, whether or not the cardiovascular events were primary or secondary endpoints. We excluded studies that only recorded all-cause mortality, after contacting the principal investigator requesting further details about cause of death when available, because the inability to determine underlying cardiovascular causes of death may lead to reporting bias.

eMethods: Qualitative Description of Trials with Active Control Groups

Six trials randomly assigned 16,857 patients to a strategy of experimental or standard influenza vaccination. Jackson et al randomized 100 patients to receive standard IM inactivated vaccine and subsequent intranasal live, attenuated vaccine and 100 patients to receive standard IM inactivated vaccine and subsequent intranasal placebo.¹ The FEVER investigators randomized 133 patients to receive standard IM vaccine and a subsequent booster of the standard vaccine among poor seroresponders, compared with 142 patients that received standard IM vaccine only without evaluation for seroresponse.² De Bruijn et al enrolled 382 participants to compare two active influenza vaccines in a 2:1 fashion, with 256 patients randomly assigned to receive an investigational IM virosomal vaccine and 126 to receive standard IM vaccine.³ Falsey et al randomized 3833 participants in a 2:1 ratio to one of two active influenza vaccine strategies, with 2573 patients treated with an investigational high-dose (4-fold increased concentration) of standard IM inactivated vaccine and 1260 treated with standard-dose IM inactivated vaccine from the same three influenza strains.⁴ Forrest et al randomized 3009 participants to one of two active influenza vaccines, 1508 patients received intranasal live, attenuated vaccine and 1501 received standard IM vaccine.⁵ DiazGranados et al randomized 9158 participants in a 2:1 ratio to one of two active influenza vaccine strategies; 6108 patients received high-dose (4-fold increased concentration) standard IM inactivated vaccine and 3050 received standard-dose IM inactivated vaccine from the same three influenza strains.⁶

eFIGURE LEGENDS

eFigure 1. Study quality and risk of bias for each eligible trial using the Cochrane criteria.

Abbreviations: FEVER: Flu-Effect of Vaccine in Elderly Residents; FLUCAD: FLU Vaccination Coronary Artery Disease; FLUVACS: FLU Vaccination Acute Coronary Syndromes; IVCAD: Influenza Vaccine for Coronary Artery Disease.

eFigure 2. Major adverse cardiovascular events comparing influenza vaccine versus control including unpublished data. Abbreviations: FLUCAD: FLU Vaccination Coronary Artery Disease; FLUVACS: FLU Vaccination Acute Coronary Syndromes; IVCAD: Influenza Vaccine for Coronary Artery Disease; M-H: Mantel-Haenszel. Square data markers represent risk ratios (RR) and horizontal lines the 95% confidence intervals (CI) with marker size reflecting the statistical weight of the study using random-effects meta-analysis. A diamond data marker represents the overall RR and 95% CI for the outcome of interest.

eFigure 3. Major adverse cardiovascular events comparing influenza vaccine versus control stratified by timing of acute coronary syndrome including unpublished data. Abbreviations: ACS: acute coronary syndrome; FLUCAD: FLU Vaccination Coronary Artery Disease; FLUVACS: FLU Vaccination Acute Coronary Syndromes; IVCAD: Influenza Vaccine for Coronary Artery Disease; M-H: Mantel-Haenszel. Square data markers represent risk ratios (RR) and horizontal lines the 95% confidence intervals (CI) with marker size reflecting the statistical weight of the study using random-effects meta-analysis. Diamond data markers represent each subgroup and overall RR and 95% CI for the outcome of interest.

eFigure 4. Cardiovascular mortality comparing influenza vaccine versus control stratified by timing of acute coronary syndrome. Abbreviations: ACS: acute coronary syndrome; FLUCAD: FLU Vaccination Coronary Artery Disease; FLUVACS: FLU Vaccination Acute Coronary Syndromes; M-H: Mantel-Haenszel. Square data markers represent risk ratios (RR) and horizontal lines the 95% confidence intervals (CI) with marker size reflecting the statistical weight of the study using random-effects meta-analysis. Diamond data markers represent each subgroup and overall RR and 95% CI for the outcome of interest.

eFigure 5. Cardiovascular mortality comparing influenza vaccine versus control including unpublished data. Abbreviations: FLUCAD: FLU Vaccination Coronary Artery Disease; FLUVACS: FLU Vaccination Acute Coronary Syndromes; IVCAD: Influenza Vaccine for Coronary Artery Disease; M-H: Mantel-Haenszel. Square data markers represent risk ratios (RR) and horizontal lines the 95% confidence intervals (CI) with marker size reflecting the statistical weight of the study using random-effects meta-analysis. A diamond data marker represents the overall RR and 95% CI for the outcome of interest.

eFigure 6. Cardiovascular mortality comparing influenza vaccine versus control stratified by timing of acute coronary syndrome including unpublished data. Abbreviations: ACS: acute coronary syndrome; FLUCAD: FLU Vaccination Coronary Artery Disease; FLUVACS: FLU Vaccination Acute Coronary Syndromes; IVCAD: Influenza Vaccine for Coronary Artery Disease; M-H: Mantel-Haenszel. Square data markers represent risk ratios (RR) and horizontal lines the 95% confidence intervals (CI) with marker size reflecting the statistical weight of the study using random-effects meta-analysis. Diamond data markers represent each subgroup and overall RR and 95% CI for the outcome of interest.

eFigure 7. All-cause mortality comparing influenza vaccine versus control. Abbreviations: FLUCAD: FLU Vaccination Coronary Artery Disease; FLUVACS: FLU Vaccination Acute Coronary Syndromes; IVCAD: Influenza Vaccine for Coronary Artery Disease; M-H: Mantel-Haenszel. Square data markers represent risk ratios (RR) and horizontal lines the 95% confidence intervals (CI) with marker size reflecting the statistical weight of the study using random-effects meta-analysis. A diamond data marker represents the overall RR and 95% CI for the outcome of interest.

eFigure 8. Fatal and non-fatal myocardial infarction events comparing influenza vaccine versus control. Abbreviations: FLUCAD: FLU Vaccination Coronary Artery Disease; FLUVACS: FLU Vaccination Acute Coronary Syndromes; IVCAD: Influenza Vaccine for Coronary Artery Disease; M-H: Mantel-Haenszel. Square data markers represent risk ratios (RR) and horizontal lines the 95% confidence intervals (CI) with marker size reflecting

the statistical weight of the study using random-effects meta-analysis. A diamond data marker represents the overall RR and 95% CI for the outcome of interest.

eFigure 9. Fatal and non-fatal stroke events comparing influenza vaccine versus control. Abbreviations: FLUCAD: FLU Vaccination Coronary Artery Disease; FLUVACS: FLU Vaccination Acute Coronary Syndromes; IVCAD: Influenza Vaccine for Coronary Artery Disease; M-H: Mantel-Haenszel. Square data markers represent risk ratios (RR) and horizontal lines the 95% confidence intervals (CI) with marker size reflecting the statistical weight of the study using random-effects meta-analysis. A diamond data marker represents the overall RR and 95% CI for the outcome of interest.

eFigure 10. Fatal and non-fatal heart failure events comparing influenza vaccine versus control. Abbreviations: FLUCAD: FLU Vaccination Coronary Artery Disease; FLUVACS: FLU Vaccination Acute Coronary Syndromes; IVCAD: Influenza Vaccine for Coronary Artery Disease; M-H: Mantel-Haenszel. Square data markers represent risk ratios (RR) and horizontal lines the 95% confidence intervals (CI) with marker size reflecting the statistical weight of the study using random-effects meta-analysis. A diamond data marker represents the overall RR and 95% CI for the outcome of interest.

eFigure 11. Unstable angina or cardiac ischemia hospitalizations comparing influenza vaccine versus control. Abbreviations: FLUCAD: FLU Vaccination Coronary Artery Disease; FLUVACS: FLU Vaccination Acute Coronary Syndromes; IVCAD: Influenza Vaccine for Coronary Artery Disease; M-H: Mantel-Haenszel. Square data markers represent risk ratios (RR) and horizontal lines the 95% confidence intervals (CI) with marker size reflecting the statistical weight of the study using random-effects meta-analysis. A diamond data marker represents the overall RR and 95% CI for the outcome of interest.

eFigure 12. Coronary revascularization hospitalizations comparing influenza vaccine versus control. Abbreviations: FLUCAD: FLU Vaccination Coronary Artery Disease; FLUVACS: FLU Vaccination Acute Coronary Syndromes; IVCAD: Influenza Vaccine for Coronary Artery Disease; M-H: Mantel-Haenszel. Square data markers represent risk ratios (RR) and horizontal lines the 95% confidence intervals (CI) with marker size reflecting the statistical weight of the study using random-effects meta-analysis. A diamond data marker represents the overall RR and 95% CI for the outcome of interest.

eFigure 13. Major adverse cardiovascular events comparing experimental versus standard influenza vaccine. Abbreviations: FEVER: Flu-Effect of Vaccine in Elderly Residents. Square data markers represent risk ratios (RR) and horizontal lines the 95% confidence intervals (CI) with marker size reflecting the statistical weight of the study using random-effects meta-analysis. A diamond data marker represents the overall RR and 95% CI for the outcome of interest.

eFigure 14. Funnel Plot comparing influenza vaccine to placebo or control for major adverse cardiovascular events. The outer dashed lines indicate the triangular confidence interval boundary within which 95% of studies are expected to lie in the absence of bias or heterogeneity. The dashed vertical line represents the summary treatment effect point estimate. The solid vertical line represents the null treatment effect boundary. Abbreviations: FLUCAD: FLU Vaccination Coronary Artery Disease; FLUVACS: FLU Vaccination Acute Coronary Syndromes; IVCAD: Influenza Vaccine for Coronary Artery Disease.

eFigure 15. Funnel Plot comparing influenza vaccine to placebo or control for major adverse cardiovascular events stratified by timing of acute coronary syndrome. The outer dashed lines indicate the triangular confidence interval boundary within which 95% of studies are expected to lie in the absence of bias or heterogeneity. The dashed vertical line represents the summary treatment effect point estimate. The solid vertical line represents the null treatment effect boundary. Abbreviations: ACS: acute coronary syndrome; CAD: coronary artery disease; FLUCAD: FLU Vaccination Coronary Artery Disease; FLUVACS: FLU Vaccination Acute Coronary Syndromes; IVCAD: Influenza Vaccine for Coronary Artery Disease.

eFigure 16. Funnel Plot comparing influenza vaccine to placebo or control for cardiovascular mortality. The outer dashed lines indicate the triangular confidence interval boundary within which 95% of studies are expected to lie in the absence of bias or heterogeneity. The dashed vertical line represents the summary treatment effect point estimate. The solid vertical line represents the null treatment effect boundary. Abbreviations: FLUCAD: FLU

Vaccination Coronary Artery Disease; FLUVACS: FLU Vaccination Acute Coronary Syndromes; IVCAD:
Influenza Vaccine for Coronary Artery Disease.

eTABLES

eTable 1: Level of Influenza Activity Observed during each Study Period

Study	Influenza Season	Region	Level of Activity*
Govaert et al, 1994 ⁷	1991-1992	Netherlands	Regional ⁸
Jackson et al, 1999 ¹	1997	USA	Sporadic ⁹
FLUVACS, 2004 ^{10, 11}	2001-2002	Argentina	Sporadic ^{12, 13}
De Bruijn et al, 2005 ³	2001-2002	Netherlands	Sporadic ^{12, 13}
FEVER 2007 ²	2004-2005	UK	Regional ¹⁴
FLUCAD 2008 ^{15, 16}	2004-2005	Poland	Regional ¹⁴
Falsey et al, 2009 ⁴	2006-2007	USA	Regional ¹⁷
IVCAD, 2009 ¹⁸	2007-2008	Iran	NA
De Villiers et al, 2009 ¹⁹	2001-2002	South Africa	Sporadic ^{12, 13}
Phrommintikul et al, 2011 ²⁰	2007-2008	Thailand	Sporadic ²¹
	2008-2009		Widespread ²²
Forrest et al, 2011 ⁵	2002	South Africa	Sporadic ^{13, 23}
DiazGranados et al, 2013 ⁶	2009-2010	USA	Widespread ^{24, 25}

Abbreviations: FEVER: Flu-Effect of Vaccine in Elderly Residents; FLUCAD: FLU Vaccination Coronary Artery Disease; FLUVACS: FLU Vaccination Acute Coronary Syndromes; IVCAD: Influenza Vaccine for Coronary Artery Disease; NA: not available; UK: United Kingdom; USA: United States of America. *Levels of influenza activity according to the Centers for Disease Control and Prevention and World Health Organization reports cataloged at www.who.int/flunet are categorized as 1) no activity; 2) sporadic: isolated laboratory-confirmed influenza cases or a laboratory-confirmed outbreak in one institution, with no increase in activity; 3) local: increased incidence of influenza-like illness (ILI), or >1 institutional outbreak of ILI or laboratory-confirmed influenza in one region with recent laboratory evidence of influenza in that region; virus activity no greater than sporadic in other regions; 4) regional: outbreaks of ILI or laboratory-confirmed influenza in >1 region with a combined population of < 50% of the state's total population; and 5) widespread: outbreaks of ILI or laboratory-confirmed influenza in >50% of the regions in the state.

eTable 2: Cardiovascular Outcomes and Duration of Follow-up Among Included Studies

Study (Year)	Cardiovascular Outcomes	Follow-up (months)
Govaert et al, 1994 ⁷	CV death, MI, and stroke	5
Jackson et al, 1999 ¹	UA, stroke, and HF	1
FLUVACS, 2004 ^{10, 11}	CV death, MI, and hospitalization for severe recurrent ischemia	12
De Bruijn et al, 2005 ³	CV death, MI, and HF	6
FEVER, 2007 ²	CV death	8
FLUCAD, 2008 ^{15, 16}	CV death, MI, coronary revascularization, and hospitalization for myocardial ischemia	12
Falsey 2009 ⁴	Fatal and non-fatal MI and stroke	6
IVCAD 2009 ¹⁸	CV death, MI, UA, and coronary revascularization	12
De Villiers et al, 2009 ¹⁹	CV death, MI, UA, HF, and stroke	8
Phrommintikul et al, 2011 ²⁰	CV death, MI, UA, HF, and stroke	12
Forrest et al, 2011 ⁵	CV death, MI, stroke	8
DiazGranados et al, 2013 ⁶	Fatal and non-fatal MI and stroke	6

Abbreviations: CV: cardiovascular; FEVER: Flu-Effect of Vaccine in Elderly Residents; FLUCAD: FLU Vaccination Coronary Artery Disease; FLUVACS: FLU Vaccination Acute Coronary Syndromes; HF: heart failure; IVCAD: Influenza Vaccine for Coronary Artery Disease; MI: myocardial infarction; UA: unstable angina.

eTable 3: Study Quality and Risk of Bias for Each Eligible Trial using the Jadad Score

Study (Year)	Randomization	Adequate Randomization Method Described	Double-Blind Trial	Adequate Blinding Method Described	Patient Attrition and Reasons Described	Total Score	Quality
Govaert et al, 1994 ⁷	Yes	No	Yes	Yes	Yes	4	High
Jackson et al, 1999 ¹	Yes	Yes	Yes	No	Yes	4	High
FLUVACS, 2004 ^{10, 11}	Yes	No	No	No	Yes	2	Low
De Bruijn et al, 2005 ³	Yes	No	No	No	Yes	2	Low
FEVER, 2007 ²	Yes	Yes	No	No	Yes	3	High
FLUCAD, 2008 ^{15, 16}	Yes	Yes	Yes	Yes	Yes	5	High
Falsey 2009 ⁴	Yes	Yes	Yes	Yes	Yes	5	High
IVCAD 2009 ¹⁸	Yes	No	No	No	No	1	Low
De Villiers et al, 2009 ¹⁹	Yes	Yes	Yes	Yes	Yes	5	High
Phrommintikul et al, 2011 ²⁰	Yes	Yes	No	No	Yes	3	High
Forrest et al, 2011 ⁵	Yes	Yes	No	No	Yes	3	High
DiazGranados et al, 2013 ⁶	Yes	Yes	Yes	Yes	Yes	5	High

The Jadad quality and risk of bias score includes two items directly related to bias reduction (randomization and double-blind design) and three items representing the quality of reporting of trial design and follow-up (including patient attrition). The scale elicits a present (yes) or absent (no) response for each item. The sum of all present items produces a score ranging from 0 to 5, with a score of 3 or higher indicative of a high quality trial.²⁶ Abbreviations: FEVER: Flu-Effect of Vaccine in Elderly Residents; FLUCAD: FLU Vaccination Coronary Artery Disease; FLUVACS: FLU Vaccination Acute Coronary Syndromes; IVCAD: Influenza Vaccine for Coronary Artery Disease.

eTable 4: Sensitivity Analyses of Major Adverse Cardiovascular Events Comparing Influenza Vaccine Versus Control

Model	Risk Ratio (95% CI)	P-value
Random Effects	0.64 (0.48-0.86)	0.003
Fixed Effects	0.63 (0.50-0.80)	0.0002
Yusuf-Peto	0.59 (0.45-0.77)	0.0001
Random Effects Model Results with Addition of Unpublished Trial		
IVCAD, 2009 ¹⁸	0.64 (0.49-0.84)	0.001
Random Effects Model Results after Individual Removal of Each Trial		
Govaert et al, 1994 ⁷	0.62 (0.48-0.78)	<0.0001
FLUVACS, 2004 ^{10,11}	0.69 (0.48-1.00)	0.05
FLUCAD, 2008 ^{15,16}	0.68 (0.50-0.94)	0.02
IVCAD, 2009 ¹⁸	0.64 (0.48-0.86)	0.003
De Villiers et al, 2009 ¹⁹	0.59 (0.46-0.76)	<0.0001
Phromminitkul et al, 2011 ²⁰	0.69 (0.52-0.91)	0.01

Abbreviations: FLUCAD: FLU Vaccination Coronary Artery Disease; FLUVACS: FLU Vaccination Acute Coronary Syndromes; IVCAD: Influenza Vaccine for Coronary Artery Disease.

eTable 5: Major Adverse Cardiovascular Events Comparing Influenza Vaccine Versus Control according to Selected Subgroups

Baseline Characteristics	Subgroup	Influenza Vaccine		Placebo/Control		Risk Ratio (95% CI)	P-interaction
		No. of Events	No. at Risk	No. of Events	No. at Risk		
History of ACS	ACS ≤ 1 year	43	414	91	401	0.46 (0.33-0.64)	0.03
	Stable CAD	21	412	25	428	0.91 (0.54-1.54)	
Number of Patients	≥ 400	63	3093	97	3084	0.68 (0.44-1.06)	0.72
	< 400	35	280	57	278	0.62 (0.43-0.89)	
Duration of Follow-up	< 6 months	7	927	5	911	1.38 (0.44-4.32)	0.17
	≥ 6 months	91	2446	149	2451	0.61 (0.48-0.78)	
Influenza Activity	High	23	1252	35	1244	0.76 (0.32-1.80)	0.70
	Low	72	1986	116	1987	0.63 (0.43-0.91)	
Cardiovascular Outcome	Efficacy	71	826	129	829	0.56 (0.43-0.73)	0.03
	Safety	27	2547	25	2533	1.08 (0.63-1.85)	
Trial Quality	High	36	1945	50	1955	0.73 (0.41-1.33)	0.55
	Low	62	1428	104	1407	0.60 (0.44-0.82)	
Control Type	Placebo	46	3007	58	2997	0.80 (0.54-1.18)	0.14
	None	52	366	96	365	0.55 (0.41-0.74)	

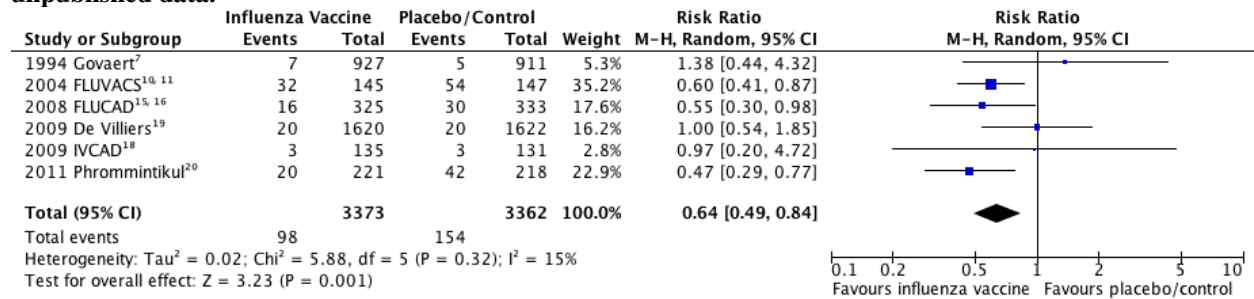
Abbreviations: ACS: acute coronary syndrome; CAD: coronary artery disease; CI: confidence intervals.

eFIGURES

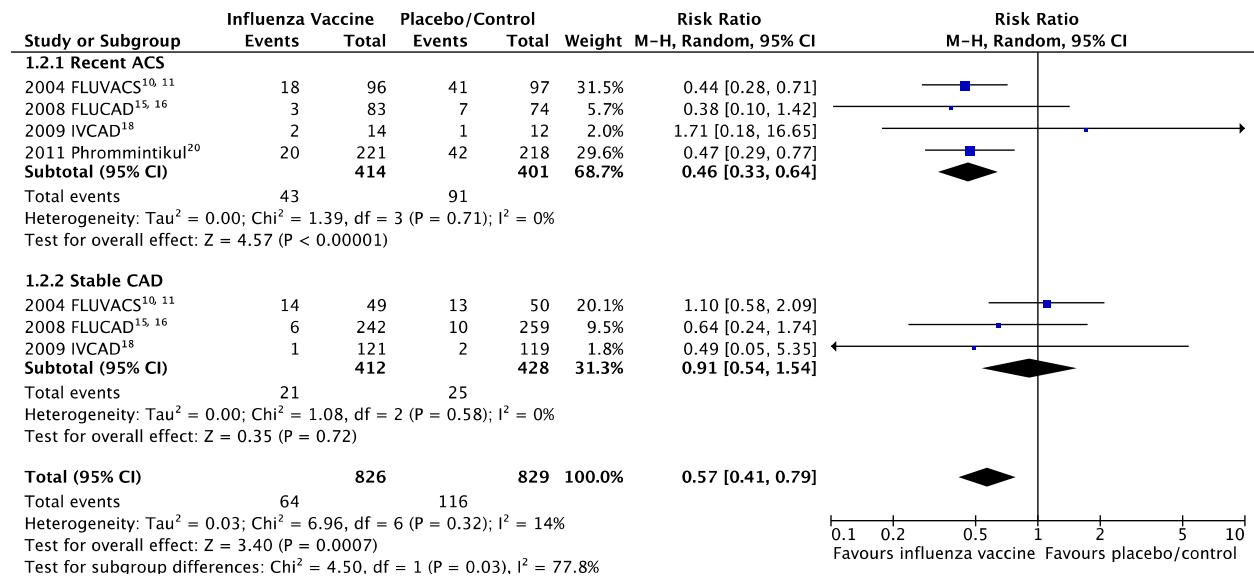
eFigure 1. Study quality and risk of bias for each eligible trial using the Cochrane criteria.

	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)	Selective reporting (reporting bias)	Other bias
1994 Govaert ⁷	?	+	+	+	-	+	+
1999 Jackson ¹	+	+	+	?	+	-	?
2004 FLUVACS ^{10, 11}	?	?	-	+	+	+	+
2005 de Bruijn ³	?	?	-	-	-	-	+
2007 FEVER ²	+	+	-	+	+	+	+
2008 FLUCAD ^{15, 16}	+	+	+	+	+	+	+
2009 De Villiers ¹⁹	+	+	+	+	+	+	?
2009 Falsey ⁴	+	+	+	+	+	-	+
2009 IVCAD ¹⁸	-	-	-	-	+	+	?
2011 Forrest ⁵	+	-	-	?	+	+	?
2011 Phrommintikul ²⁰	+	-	-	+	+	+	?
2013 DiazGranados ⁶	+	+	+	+	+	?	+

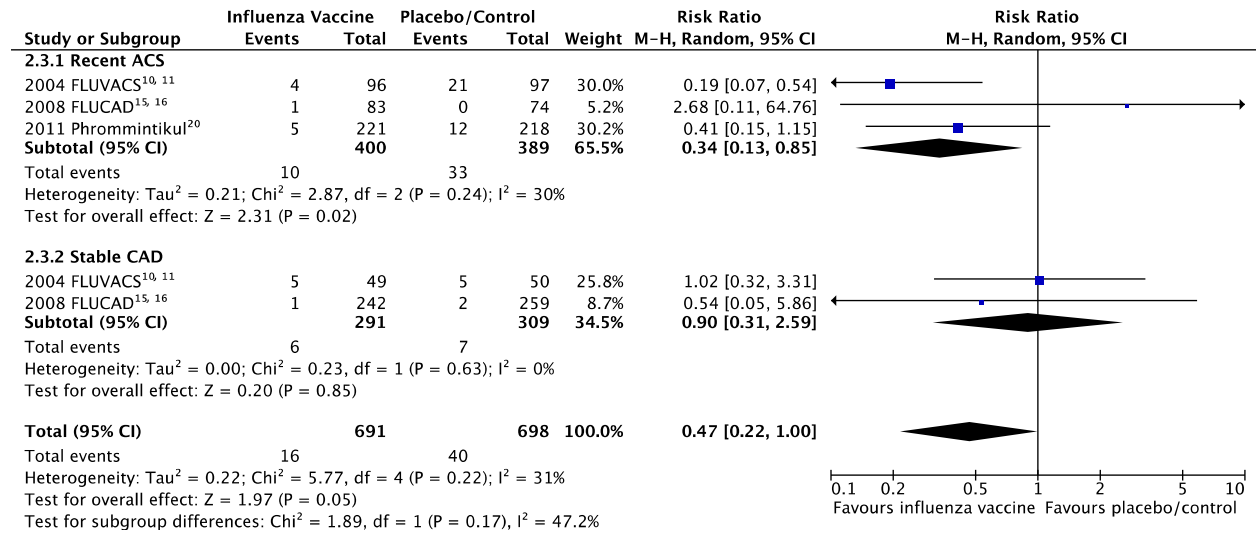
eFigure 2. Major adverse cardiovascular events comparing influenza vaccine versus control including unpublished data.



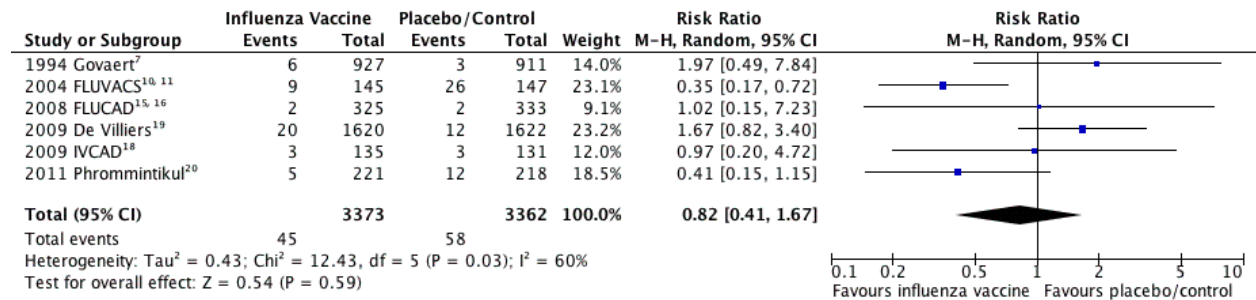
eFigure 3. Major adverse cardiovascular events comparing influenza vaccine versus control stratified by timing of acute coronary syndrome including unpublished data.



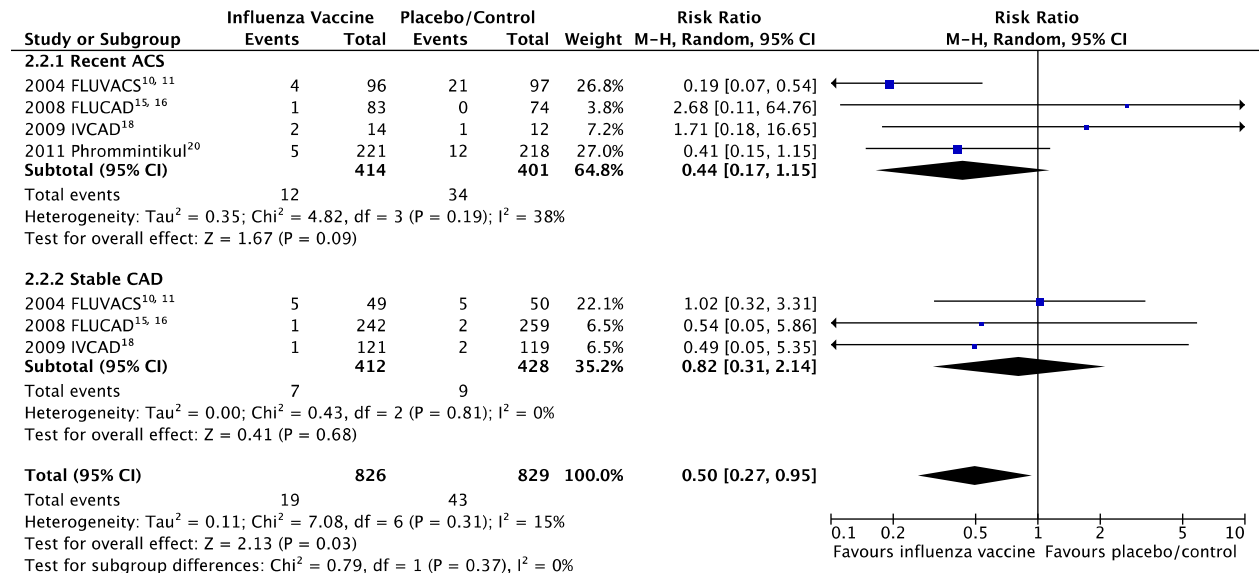
eFigure 4. Cardiovascular mortality comparing influenza vaccine versus control stratified by timing of acute coronary syndrome.



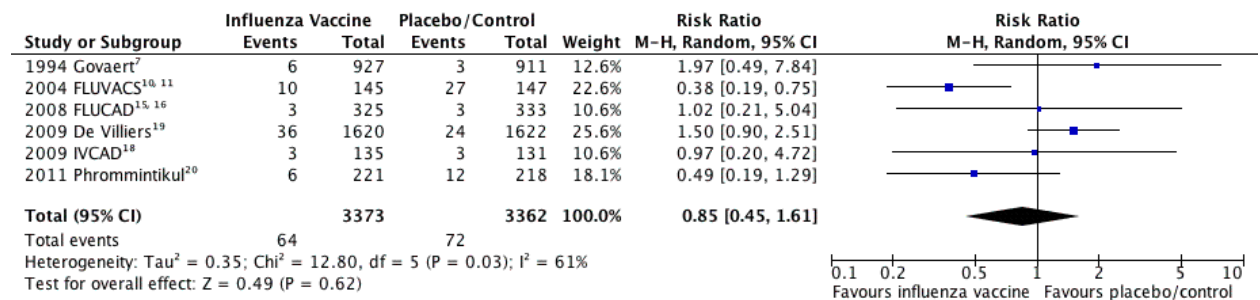
eFigure 5. Cardiovascular mortality comparing influenza vaccine versus control including unpublished data.



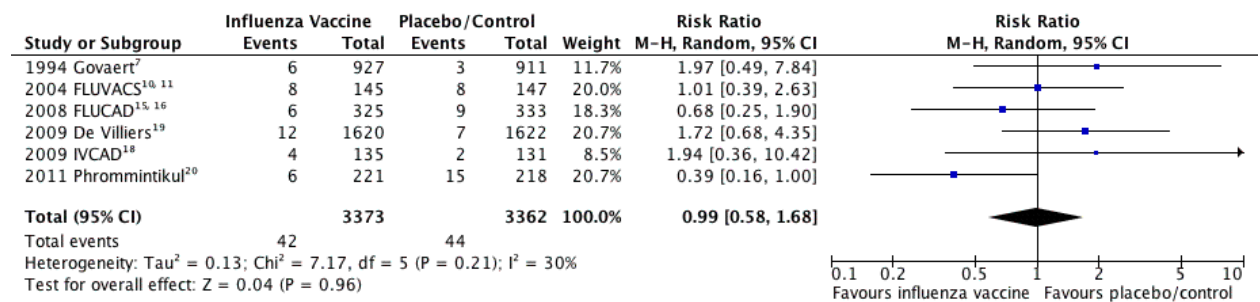
eFigure 6. Cardiovascular mortality comparing influenza vaccine versus control stratified by timing of acute coronary syndrome including unpublished data.



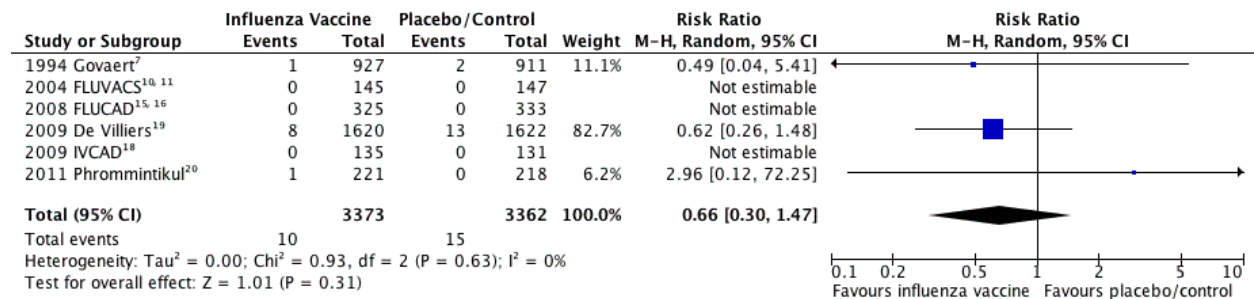
eFigure 7. All-cause mortality comparing influenza vaccine versus control.



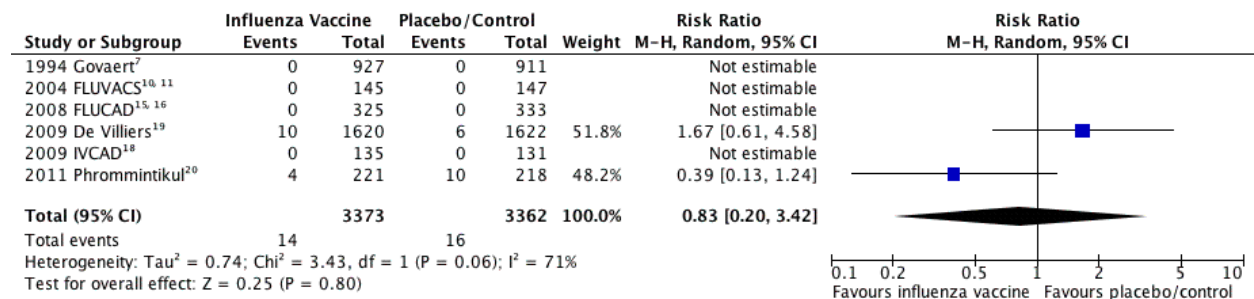
eFigure 8. Fatal and non-fatal myocardial infarction events comparing influenza vaccine versus control.



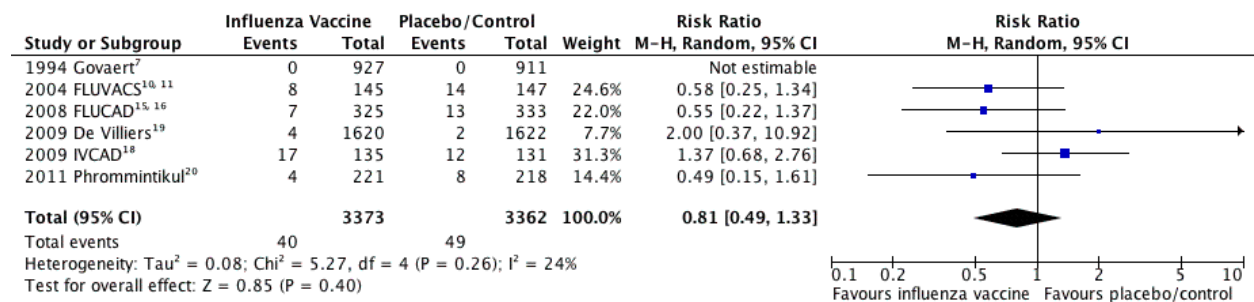
eFigure 9. Fatal and non-fatal stroke events comparing influenza vaccine versus control.



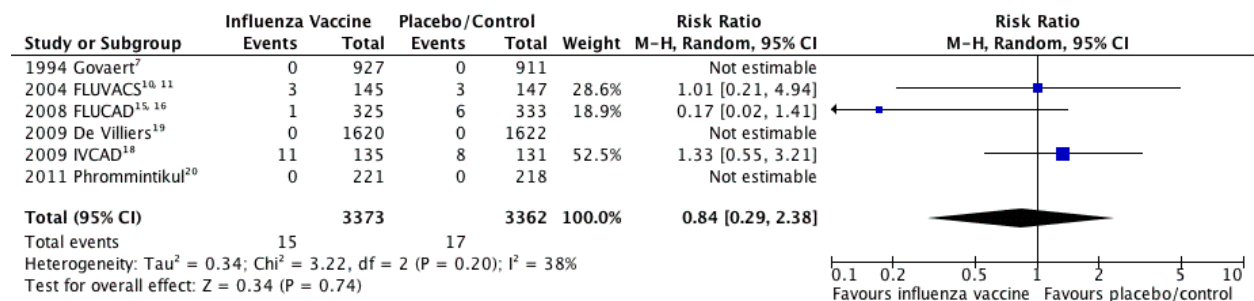
eFigure 10. Fatal and non-fatal heart failure events comparing influenza vaccine versus control.



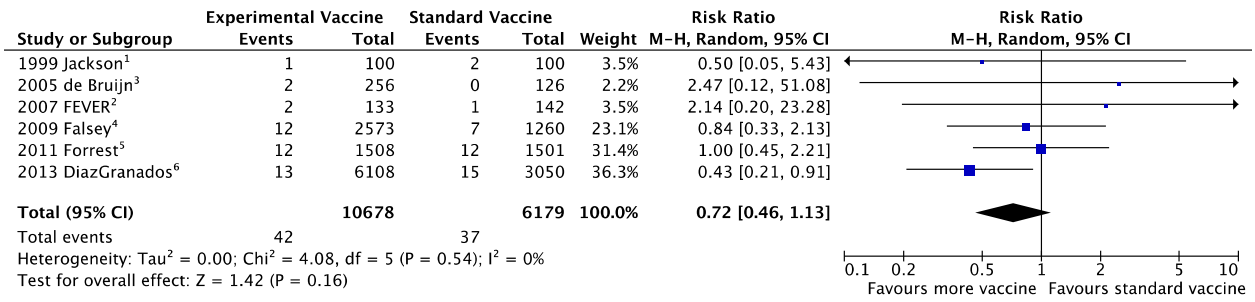
eFigure 11. Unstable angina or cardiac ischemia hospitalizations comparing influenza vaccine versus control.



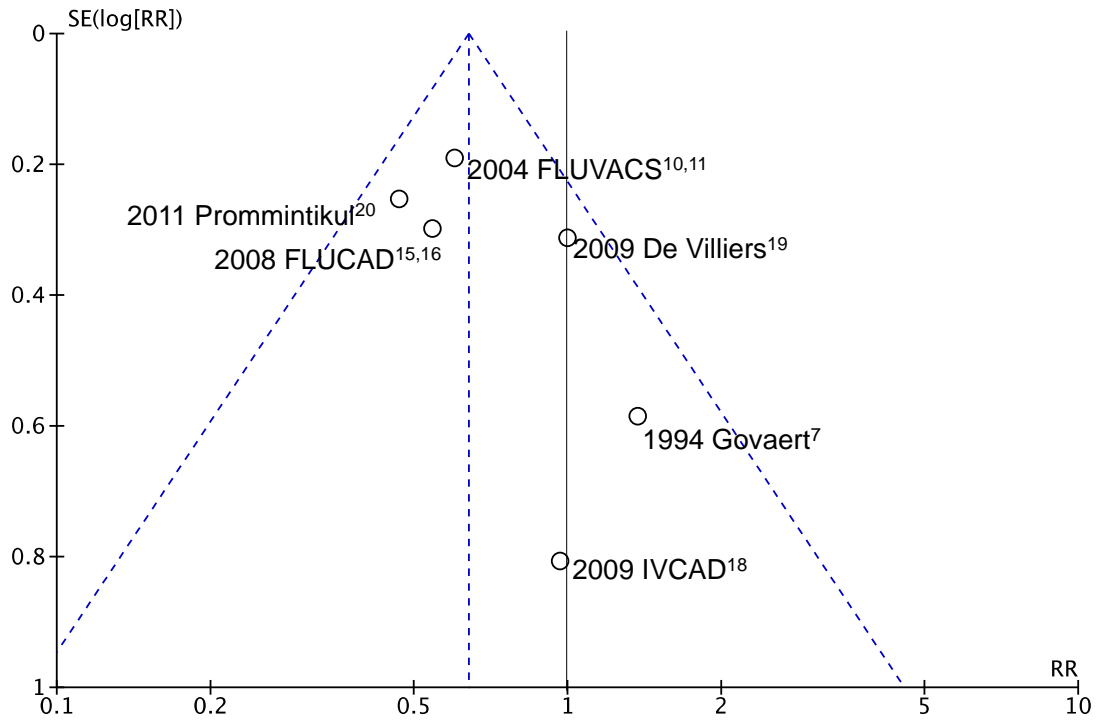
eFigure 12. Coronary revascularization hospitalizations comparing influenza vaccine versus control.



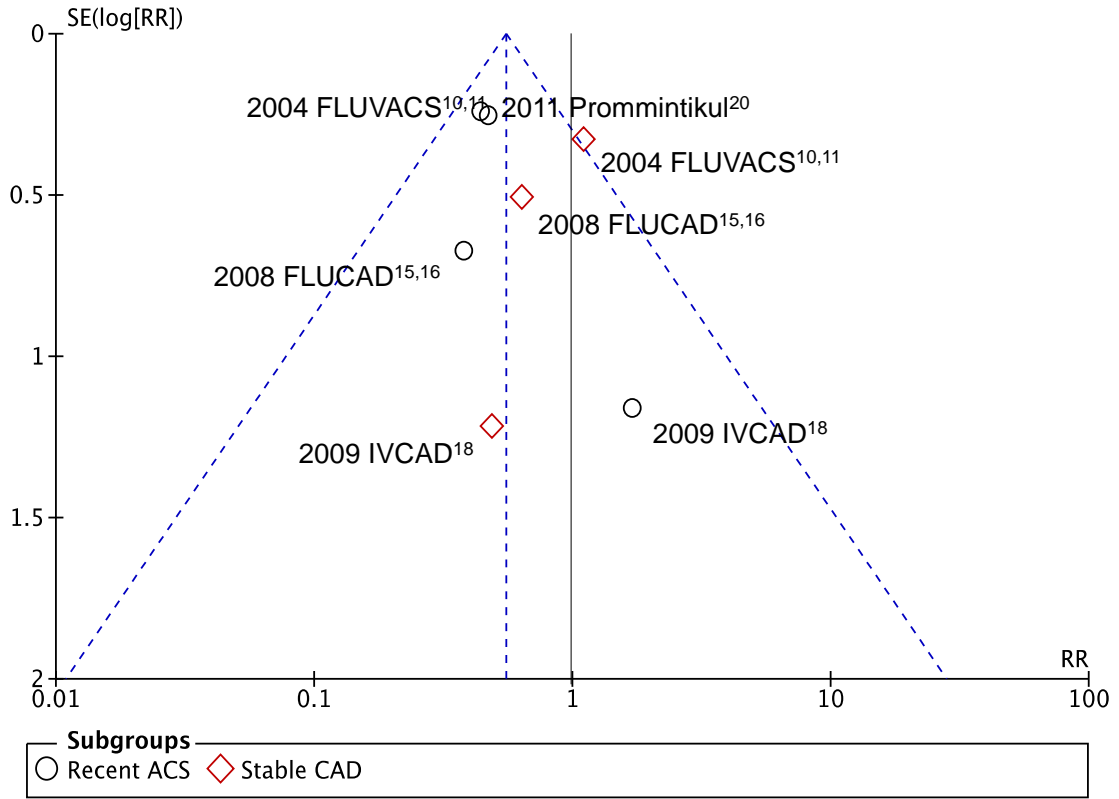
eFigure 13. Major adverse cardiovascular events comparing experimental versus standard influenza vaccine.



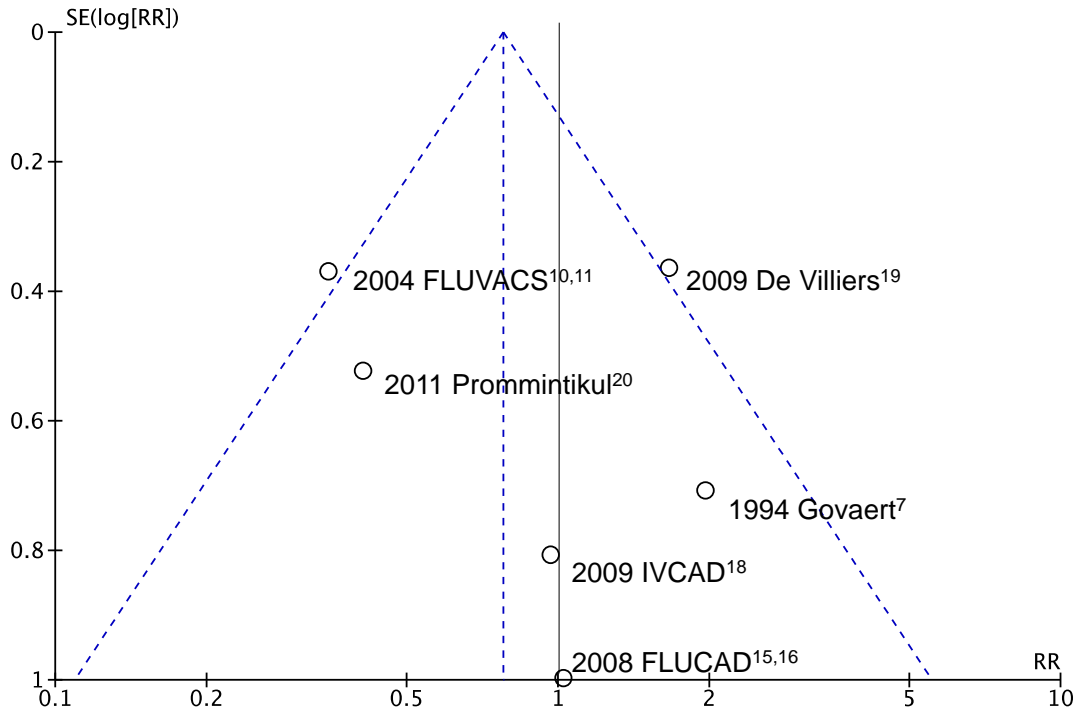
eFigure 14. Funnel Plot comparing influenza vaccine to placebo or control for major adverse cardiovascular events.



eFigure 15. Funnel Plot comparing influenza vaccine to placebo or control for major adverse cardiovascular events stratified by timing of acute coronary syndrome.



eFigure 16. Funnel Plot comparing influenza vaccine to placebo or control for cardiovascular mortality.



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