Original research

Influenza vaccine and risk of acute myocardial infarction in a population-based case–control study

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ABSTRACT

Objective To assess the relationship between influenza vaccination and risk of a first acute myocardial infarction (AMI) in the general population by different epidemic periods.

Methods This is a population-based case–control study carried out in BIFAP (Base de datos para la investigación farmacoepidemiológica en atención primaria), over 2001–2015, in patients aged 40–99 years. Per each incident AMI case, five controls were randomly selected, individually matched for exact age, sex and index date (AMI diagnosis). A patient was considered vaccinated when he/she had a recorded influenza vaccination at least 14 days before the index date within the same season. The association between influenza vaccination and AMI risk was assessed through a conditional logistic regression, computing adjusted ORs (AOR) and their respective 95% CIs. The analysis was performed overall and by each of the three time epidemic periods per study year (pre-epidemic, epidemic and postepidemic).

Results We identified 24 155 AMI cases and 120 775 matched controls. Of them, 31.4% and 31.2%, respectively, were vaccinated, yielding an AOR of 0.85 (95% CI 0.82 to 0.88). No effect modification by sex, age and background cardiovascular risk was observed. The reduced risk of AMI was observed shortly after vaccination and persisted over time. Similar results were obtained during the pre-epidemic (AOR=0.87; 95% CI 0.79 to 0.95), epidemic (AOR=0.89; 95% CI 0.82 to 0.96) and postepidemic (AOR=0.83; 95% CI 0.79 to 0.87) periods. No association was found with pneumococcal vaccine (AOR=1.10; 95% CI 1.06 to 1.15).

Conclusions Results are compatible with a moderate protective effect of influenza vaccine on AMI in the general population, mostly in primary prevention, although bias due to unmeasured confounders may partly account for the results.

INTRODUCTION

Influenza causes epidemic waves that in temperate countries occur mainly during wintertime. The infection itself and its complications are the cause of a significant part of the excess winter mortality observed in these regions.[1] A relationship between influenza and increased cardiovascular (CV) morbidity and mortality has been suspected for long,[2] partially due to an increased incidence of acute myocardial infarction (AMI).[3–5] Recently, our group has published that both influenza and cold temperature are independently associated with type 1 myocardial infarction,[6] demonstrating the association between influenza and rupture of atheromatous plaques. This may explain why the risk of AMI associated with influenza is higher than that associated with other infections. As a logical consequence, the prevention of influenza infection with the vaccine should have benefits, although its empirical demonstration has proven challenging so far.

Many studies have shown a reduction in the risk of death in vaccinated persons, some in general senior population[7–9] and many others in high-risk population,[9] but their results have been questioned for inconsistencies both in terms of the magnitude of the effect and the timing of the benefit.[10] Several types of bias (ie, healthy user bias, healthy period bias) and unmeasured confounding factors (ie, frailty, poor functionality) have been alleged to partly account for the apparent protection found.[10–13] As far as AMI is concerned, three meta-analyses, including studies with different designs (case–control,[3] self-control case series (SCCS)[13] and randomised clinical trials (RCTs)/observational studies[9]) and in different populations (mostly in high-risk patients), broadly suggested a reduced risk, although it is possible that the aforementioned biases could partly account for the beneficial effect. Of note, none of them analysed the data by different time periods (before, during and after influenza waves), as suggested to detect the presence of a hidden bias.[10 12] If influenza vaccine reduces the risk of AMI, it is likely that it does so via prevention of influenza infection. Thus, we postulate that the effect of the influenza vaccine on risk of AMI will be larger during influenza epidemic periods.

It is important to stress that influenza vaccination is included in clinical practice guidelines for secondary prevention of CV disease (with a moderate level of evidence),[14 15] whereas for primary prevention the evidence is scarce and there is no clear-cut recommendations.[16]

The aim of the present study was to gauge the relationship between influenza vaccination and the risk of a first AMI in the general population taking into account the different time periods with respect to influenza epidemic waves (pre-epidemic, epidemic and postepidemic). As several studies did not show a protective effect of pneumococcal vaccine on AMI,[17] we also explored the association

of pneumococcal vaccine and AMI as a negative exposure control to further assess the risk of bias linked to vaccination.

PATIENTS AND METHODS

Study design

We carried out a nested case–control study using BIFAP (Base de datos para la investigación farmacoepidemiológica en atención primaria), a Spanish population-based database containing primary care medical information, widely used for pharmacoepidemiological research (online supplemental methods).[18]

We first constructed a primary cohort composed of all patients registered in BIFAP from 2002 to 2015 who met the following inclusion criteria: (1) aged 40–99 years; (2) had a record of at least 1 year with their primary care physician (PCP), to ensure quality of information recording; and (3) had no previous record of cancer or AMI (only incident cases were considered). A total of 3 764 470 patients were followed up until the earliest of the following events: an incident AMI, 100 years of age, a record of cancer, death or the end of the study period.

Selection of cases and controls

All potential cases of AMI in the primary cohort were identified using International Classification of Primary Care-2 code K75 (acute myocardial infarction), International Classification of Diseases-9-Clinical Modification code 410.9 (myocardial infarction) and related terms (free text) in diagnosis fields. Subsequently, these potential cases were subjected to a validation procedure which yielded a positive predictive value of 87.2% (95% CI 84.1% to 89.8%) (online supplemental methods). For each case, the index date was established as the date of AMI diagnosis. Matched controls (by age, sex and index date) were randomly selected following a risk set sampling from the underlying cohort. Then, controls had the same index date as their matched case.

Time period definition

Each study year was defined from 1 September through 31 August, which was subsequently divided into three different periods[10]: (1) pre-epidemic: from 1 September to the beginning of the influenza epidemic wave; (2) epidemic: the epidemic wave period defined by the Spanish Influenza Surveillance System (https://vgripe.isciii.es/inicio.do); and (3) postepidemic: from the end of the epidemic wave to the end of the study year (31 August) (dates and the main characteristics per each study year are in online supplemental table 1). In a secondary analysis we used only two periods: influenza season (from week 40 to week 20 next year) and non-influenza season (from week 21 to week 39).

As the influenza vaccination campaign usually starts in week 40 (first week of October), we redefined, in a sensitivity analysis, the study year from week 40 to week 39 and modified accordingly the pre-epidemic and postepidemic periods.

Exposure definition

Patients were considered to be vaccinated against influenza when they received the vaccine beyond 14 days prior to the index date within the same study year (the time needed to develop an immune response) (https://www.ecdc.europa.eu/en/seasonal-influenza/prevention-and-control/vaccines/timing). To appraise the risk of AMI since the time of vaccination, different time windows were established (days 15–30, and thereafter every 30 days). A patient was considered exposed to the pneumococcal vaccine if he/she had a record ever before 14 days of the index date.

Potential confounding factors

The following variables recorded prior to the index date were considered as potential confounding factors: (1) *comorbidities:* cerebrovascular accident (ischaemic, haemorrhagic or non-specified stroke and transient ischaemic attack), heart failure, angina pectoris (recorded as such and/or use of nitrates), peripheral artery disease, hypertension, diabetes (recorded as such and/or use of glucose-lowering drugs), dyslipidaemia (recorded as such and/or use of lipid-lowering drugs), chronic obstructive pulmonary disease, rheumatoid arthritis, osteoarthritis, chronic kidney failure and hyperuricaemia (asymptomatic and gout); (2) *lifestyle factors:* body mass index (BMI) and smoking status; (3) number of visits to the PCP in the year prior to the index date; and (4) recorded use of the following drugs in the 30 days prior to the index date: antiplatelet drugs, oral anticoagulants, paracetamol, metamizole, non-steroidal anti-inflammatory drugs, corticosteroids, ACE inhibitors, angiotensin II receptor blockers, calcium-channel blockers, beta-blockers, alfa-blockers, diuretics and proton pump inhibitors.

Among controls, we examined the distribution of all these factors according to the influenza vaccination status in order to assess whether vaccinated subjects were healthier than non-vaccinated, as previously suggested.[10 13]

Statistical analysis

We applied a conditional regression model to estimate the OR and the corresponding 95% CI of the association between influenza vaccination and incident AMI. First, we estimated the crude ORs including only the exposure; in the second step, we computed the adjusted OR (AOR) adding all the potential confounding factors mentioned above. The postulated causal diagrams are shown in online supplemental figure 1.

Moreover, we considered a possible interaction with gender, age (stratified as less than 65 and equal or greater than 65 years old) and baseline CV risk. For the latter, we established three risk categories as follows: (1) high risk: patients with a history of angina pectoris, peripheral arterial disease, stroke or diabetes; (2) intermediate risk: those with a record of hypertension, dyslipidaemia, chronic renal failure, current smoking or BMI >30 kg/m^2 (and none of the CV diseases pointed out in the first item); and (3) low risk: the remainder. To assess whether there was a statistical interaction we applied the test described by Altman and Bland[19] to compare AORs across strata. For the stratified analysis by CV risk we performed an unconditional logistic regression including the matching variables in the model because conditional logistic regression provided unstable estimates.

To address missing values for smoking (50.8%) and BMI (39.6%), we run multiple imputation by chained equations models in all analyses (online supplemental methods).

We conducted all analyses using STATA V.15/SE.

Patient and public involvement

Patients were not involved in the design, conduct, reporting or dissemination plans of our research.

RESULTS

From a primary base of 3.7 million patients attended by PCPs, we identified 24 155 valid incident cases of AMI and randomly extracted a total of 120 775 matched controls; 30.6% of cases fell in the pre-epidemic period (139.44 cases per 4 weeks),

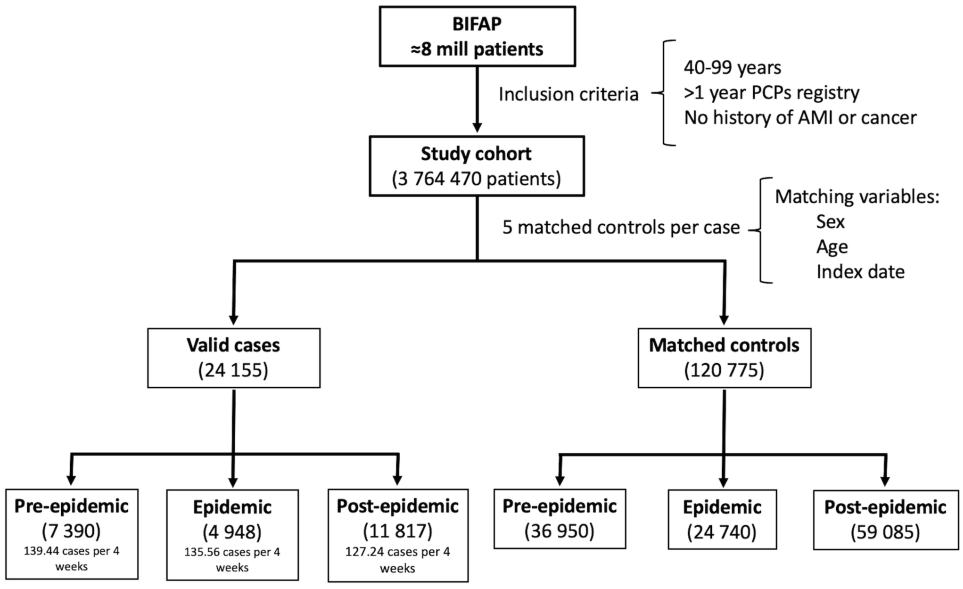

Figure 1 Flow chart of patient selection. AMI, acute myocardial infarction; BIFAP, Base de datos para la investigación farmacoepidemiológica en atención primaria; PCP, primary care physician.

20.5% in the epidemic period (135.56 cases per 4 weeks) and 48.9% (127.24 cases per 4 weeks) in the postepidemic period (figure 1).

The characteristics of cases and controls are shown in table 1. As expected, cases presented a higher prevalence of CV risk factors and comedication, as well as a greater number of visits to the PCP in the last 12 months prior to the index date, than their matched controls. Among controls, the vaccinated subjects presented a higher prevalence of CV diseases and risk factors, as well as a heavier use of comedication, than unvaccinated subjects (figure 2 and online supplemental table 2); consistently, the proportion of subjects with more than 16 visits to their PCP in the last year before the index date was higher (43.3%) in vaccinated as compared with unvaccinated subjects (19.0%). The difference was even greater in subjects younger than 65 years old (online supplemental figure 2).

Most people were vaccinated between 38 and 49 weeks, with no difference among cases and controls (online supplemental figure 3). The proportion of vaccinated subjects among cases was 31.41% as compared with 31.22% among controls, yielding a crude OR of 1.01 (95% CI 0.98 to 1.05), which went down to 0.85 (95% CI 0.82 to 0.88) when fully adjusted for CV risk factors and comedication (table 2). The association of influenza vaccination with a reduced risk of AMI was similar across different time periods according to the epidemic waves, showing no significant interaction by period (test of interaction: p=0.713 for pre-epidemic vs epidemic and p=0.139 for postepidemic vs epidemic) (table 2).

When the study year was redefined ranging from week 40 to week 39, we found an AOR of 0.88 (95% CI 0.82 to 0.95), 0.92 (95% CI 0.85 to 1.00) and 0.85 (95% CI 0.81 to 0.90) for the pre-epidemic, epidemic and postepidemic period, respectively (online supplemental table 3).

The overall risk reduction of AMI among vaccinated persons was observed in all subgroups examined (by sex, age and background CV risk) (figure 3 and online supplemental table 4). No statistically significant interaction was detected.

The reduced risk of AMI associated with vaccination appears shortly after vaccination and persisted over time (figure 4). This pattern was observed in all subgroups examined (by age, sex and background CV risk) (online supplemental table 5).

No association was found between pneumococcal vaccination and AMI overall (AOR=1.10; 95% CI 1.06 to 1.15) (table 3) or in any time window since vaccination (online supplemental table 6).

DISCUSSION

The main findings of the present study are as follows: (1) influenza vaccination was associated with a reduced risk of AMI of around 10%–15%; (2) such a reduced risk was present in all subgroups examined (by sex, age and background CV risk); (3) the risk reduction associated with vaccination appears to be similar regardless of the epidemic time period, which suggests that other factors different from the prevention of influenza infection might partly account for the results found, including the possibility of bias; and (4) we did not find a decreased risk of AMI in subjects who received the pneumococcal vaccine.

Our results are consistent with those found by other epidemiological studies using different designs. In a meta-analysis of RCTs carried out in high-risk patients, Udell *et al*[20] estimated an relative risk (RR) of major adverse cardiovascular events (MACE) associated with influenza vaccine of 0.64 (95% CI 0.48 to 0.86). In a meta-analysis of case–control studies, Barnes *et al*[3] pooled seven studies including patients with AMI with and without previous AMI (two of them population-based and five hospital-based) and obtained a risk reduction of 29% (95% CI 9% to 44%). Chiang *et al*[21] carried out a population-based case–control study in elderly patients (not included in the meta-analysis) and found an AOR of 0.80 (0.76–0.84) for AMI. In a systematic review of SCCS, Caldeira *et al*[13] found two studies and estimated a pooled RR of 0.84 (95% CI 0.78 to 0.91). Not included in such meta-analysis, Sen *et al*,[22] in a nationwide SCCS carried out in Norway during the 2009 pandemic, reported an RR of 0.72 (95% CI 0.59 to 0.88) among high-risk subjects. More recently, Yedlapati *et al*[9] in a meta-analysis of different types of studies (4 RCTs and 12 observational studies), including only patients with established CV disease, found a non-significant trend to a risk reduction of AMI (RR=0.73; 95% CI 0.49 to 1.09) and a

Table 1 Characteristics of cases and controls

	Cases (%) n=24 155	Controls (%) n=120 775	Non-adjusted OR* (95% CI)
Age, mean (SD)	67.1 (±13.4)	67.0 (±13.4)	–
Men	17 208 (71.2)	86 040 (71.2)	–
Visits (last 12 months)			
Up to 5	6867 (28.43)	44 979 (37.24)	1 (ref)
6–15	9008 (37.29)	43 706 (36.19)	1.44 (1.39 to 1.49)
16–24	4498 (18.62)	18 381 (15.22)	1.81 (1.73 to 1.89)
25+	3782 (15.66)	13 709 (11.35)	2.12 (2.02 to 2.23)
BMI kg/m^2			
Up to 24.9	2721 (11.26)	14 574 (12.07)	1 (ref)
25–29	6997 (28.97)	34 041 (28.19)	1.10 (1.05 to 1.16)
30–34	4162 (17.23)	18 752 (15.53)	1.19 (1.13 to 1.26)
35–39	1122 (4.65)	4488 (3.72)	1.35 (1.25 to 1.46)
40+	334 (1.38)	1149 (0.95)	1.56 (1.38 to 1.78)
Unknown	8819 (36.51)	47 771 (39.55)	0.98 (0.94 to 1.03)
Smoking			
Never smoking	5489 (22.72)	32 176 (26.64)	1 (ref)
Current smoker	6498 (26.90)	20 135 (16.67)	2.04 (1.95 to 2.12)
Past smoker	1287 (5.33)	7067 (5.85)	1.11 (1.04 to 1.19)
Unknown	10 881 (45.05)	61 397 (50.84)	1.07 (1.03 to 1.11)
CVA			
Ischaemic	600 (2.48)	2204 (1.82)	1.39 (1.27 to 1.53)
Haemorrhagic	89 (0.37)	354 (0.29)	1.28 (1.02 to 1.62)
Unspecified	427 (1.77)	1818 (1.51)	1.20 (1.08 to 1.34)
TIA	503 (2.08)	2015 (1.67)	1.28 (1.16 to 1.42)
Heart failure	909 (3.76)	3122 (2.58)	1.50 (1.39 to 1.62)
Angina pectoris†	2735 (11.32)	5259 (4.35)	2.91 (2.77 to 3.06)
Peripheral artery disease	1092 (4.52)	2478 (2.05)	2.30 (2.14 to 2.48)
Hypertension	12 534 (51.89)	52 407 (43.39)	1.49 (1.45 to 1.53)
Diabetes‡	6543 (27.09)	19 966 (16.53)	1.92 (1.85 to 1.98)
Dyslipidaemia§	11 355 (47.01)	42 725 (35.38)	1.67 (1.62 to 1.72)
COPD	1989 (8.23)	8035 (6.65)	1.27 (1.21 to 1.34)
Rheumatoid arthritis	238 (0.99)	757 (0.63)	1.58 (1.37 to 1.83)
Osteoarthritis	2157 (8.93)	10 340 (8.56)	1.05 (1.00 to 1.10)
Chronic kidney failure	919 (3.80)	2919 (2.40)	1.62 (1.50 to 1.75)
Hyperuricaemia			
Asymptomatic	4490 (18.59)	18 071 (14.96)	1.32 (1.27 to 1.37)
Gout	1164 (4.82)	5146 (4.26)	1.20 (1.13 to 1.28)
Current use of			
Antiplatelet drugs	4793 (19.84)	14 652 (12.13)	2.05 (1.97 to 2.13)
Oral anticoagulants	921 (3.81)	5018 (4.15)	0.92 (0.85 to 0.99)
Paracetamol	2721 (11.26)	12 334 (10.21)	1.20 (1.14 to 1.26)
Metamizole	969 (4.01)	3497 (2.90)	1.50 (1.40 to 1.62)
NSAIDs	2440 (10.10)	11 103 (9.19)	1.19 (1.13 to 1.25)
Corticosteroids	523 (2.17)	1798 (1.49)	1.50 (1.35 to 1.65)
ACE inhibitors	4212 (17.44)	17 351 (14.37)	1.37 (1.32 to 1.42)
ARBs	3773 (15.62)	14 683 (12.16)	1.43 (1.37 to 1.48)
CCBs	3316 (13.73)	11 488 (9.51)	1.63 (1.56 to 1.70)
Beta-blockers	2666 (11.04)	7654 (6.34)	1.91 (1.83 to 2.01)
Alfa-blockers	609 (2.52)	2497 (2.07)	1.24 (1.13 to 1.36)
Diuretics	3112 (12.88)	12 602 (10.43)	1.38 (1.32 to 1.44)
PPIs	6494 (26.88)	25 538 (21.15)	1.53 (1.47 to 1.59)

*Adjusted only for matching factors (age, sex and calendar year).
†Recorded as such or when patients were using nitrates.
‡Recorded as such or when patients were using glucose-lowering drugs.
§Recorded as such or when patients were using lipid-lowering drugs.
ARB, angiotensin II receptor blockers; BMI, body mass index; CCB, calcium-channel blockers; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; NSAIDs, non-steroidal anti-inflammatory drugs; PPI, proton pump inhibitors; ref, reference; TIA, transient ischaemic attack.

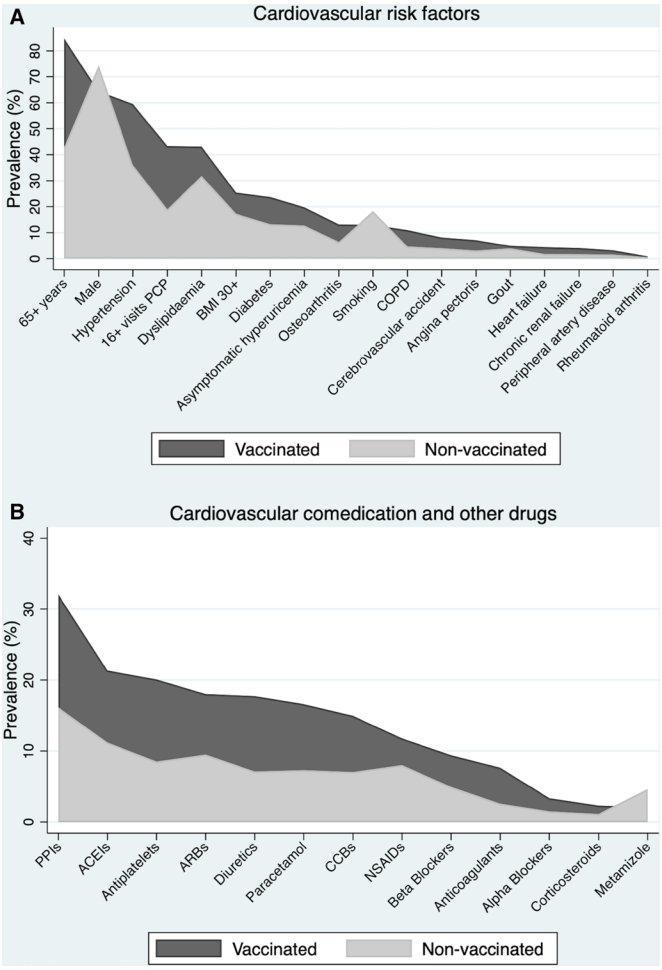

Figure 2 Distribution of cardiovascular risk factors (A) and cardiovascular comedication (B) in vaccinated as compared with unvaccinated subjects among controls (at index date). ACEIs, ACE inhibitors; ARBs, angiotensin II receptor blockers; BMI, body max index; CCBs, calcium-channel blockers; COPD, chronic obstructive pulmonary disease; NSAIDs, non-steroidal anti-inflammatory drugs; PCP, primary care physician; PPI, proton pump inhibitors.

significant reduction in CV mortality (RR=0.82; 95% CI 0.80 to 0.84) and MACE (RR=0.87; 95% CI 0.80 to 0.94). Finally, in a broad review of studies (case–control, cohort and RCTs), Cheng *et al*[23] found an RR of 0.81 (95% CI 0.76 to 0.86) for AMI (10 studies). Thus, our results are in agreement with both the direction and the magnitude of the effect shown by previous research, but an important novelty our study offers is that most patients were in a low or intermediate background CV risk, supporting the CV benefits of influenza vaccination in a primary prevention setting (not only in secondary prevention as most studies have shown). Also, no difference was found by sex and age and thus the protection suggested would be applicable to broad layers of the population.

The finding that a similar risk reduction was observed in the three epidemic periods is a puzzling result. According to our postulated causal diagrams (online supplemental figure 1), this pattern would be hardly explained uniquely by the prevention of influenza infection, and other factors, including the possibility of bias, should be considered. We can reasonably rule out the possibility that vaccinees were healthier (the so-called healthy user bias) as CV comorbidity, risk factors and comedication were more prevalent among the vaccinated than among

Table 2 Influenza vaccine and risk of acute myocardial infarction overall and by different epidemic periods

	Cases (%) N=24 155	Controls (%) N=120 775	Non-adjusted OR* (95% CI)	Adjusted OR† (95% CI)
Overall				
Non-vaccinated	16 569 (68.59)	83 065 (68.78)	1 (ref)	1 (ref)
Vaccinated	7586 (31.41)	37 710 (31.22)	1.01 (0.98 to 1.05)	0.85 (0.82 to 0.88)
	Cases (%) N=7390	**Controls (%) N=36 950**	**Non-adjusted OR* (95% CI)**	**Adjusted OR† (95% CI)**
Pre-epidemic				
Non-vaccinated	6208 (84.01)	31 089 (84.14)	1 (ref)	1 (ref)
Vaccinated	1182 (15.99)	5861 (15.86)	1.02 (0.93 to 1.10)	0.87 (0.79 to 0.95)
	Cases (%) N=4948	**Controls (%) N=24 740**	**Non-adjusted OR* (95% CI)**	**Adjusted OR† (95% CI)**
Epidemic				
Non-vaccinated	3055 (61.74)	15 517 (62.72)	1 (ref)	1 (ref)
Vaccinated	1893 (38.26)	9223 (37.28)	1.06 (0.98 to 1.14)	0.89 (0.82 to 0.96)
	Cases (%) N=11 817	**Controls (%) N=59 085**	**Non-adjusted OR* (95% CI)**	**Adjusted OR† (95% CI)**
Postepidemic				
Non-vaccinated	7306 (61.83)	36 459 (61.71)	1 (ref)	1 (ref)
Vaccinated	4511 (38.17)	22 626 (38.29)	0.99 (0.95 to 1.04)	0.83 (0.79 to 0.87)

Tests of interaction (ROR, ratio of adjusted ORs): epidemic vs pre-epidemic: ROR=1.02 (95% CI 0.91 to 1.15), p=0.713; epidemic vs postepidemic: ROR=1.07 (95% CI 0.98 to 1.18), p=0.139; pre-epidemic vs postepidemic: ROR=1.05 (95% CI 0.94 to 1.16), p=0.375.
*Adjusted only for matching factors (age, sex and calendar year).
†Adjusted for matching factors (age, sex and calendar year) plus the covariates shown in table 1.
ref, reference.

the non-vaccinated, particularly in younger subjects. Some authors[10 13] suggested a healthy period bias that may have occurred if vaccination was delayed in frail subjects; however, this possibility seems unlikely in our study for several reasons: (1) there is no difference across epidemic periods and this bias would be expected to be greater in the pre-epidemic period[10]; (2) there is no difference in the calendar time of vaccination among cases and controls (if healthier people were vaccinated earlier, we should observe a certain lag time between cases and controls) (online supplemental figure 3); and (3) frailty may be a good predictor of mortality, but as far as we know it is not a well-established predictor of an atherothrombotic event. An adherent user bias (ie, vaccinated persons may have a better adherence to their treatment and other preventive measures than the non-vaccinated) may account for a spurious reduced risk that would be present in all the three periods.[6] On the contrary, if vaccination improves survival, a greater depletion of susceptible subjects among the unvaccinated during epidemic and postepidemic periods might underestimate a potential protective effect of vaccination on AMI in those periods. Future studies should focus on these and other potential biases to elucidate their role in a potential cardioprotective effect of influenza vaccination.

Nevertheless, the lack of a reduced risk of AMI associated with the pneumococcal vaccine does not support bias as the only explanation. Further, we should bear in mind that relative risk measures are greatly influenced by the background incidence of AMI (ie, they tend to be lower as the background incidence increases) and, as it is well known, the incidence of AMI is higher in winter than during other seasons.[7 24] Thus, the effect of vaccine due to prevention of influenza infection during winter

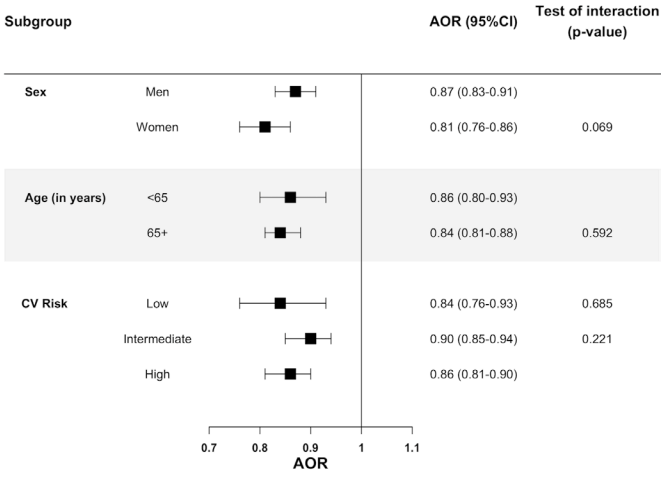

Figure 3 Influenza vaccine and risk of acute myocardial infarction by different subgroups (sex, age and background cardiovascular risk). AOR, adjusted OR; CV, cardiovascular.

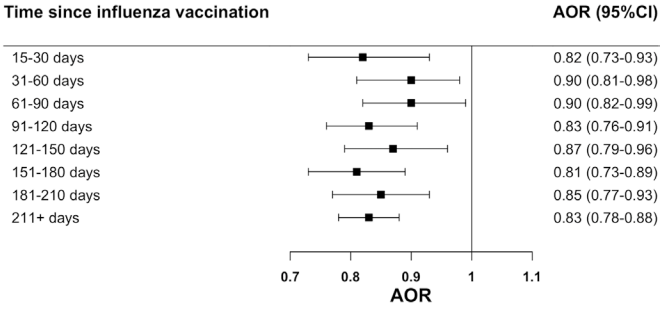

Figure 4 Risk of acute myocardial infarction associated with influenza vaccination according to time windows since vaccination. AOR, adjusted OR.

Table 3 Risk of acute myocardial infarction and previous pneumococcal vaccination (ever)

	Cases (%) n=24 155	Controls (%) n=120 115	Non-adjusted OR* (95% CI)	Adjusted OR† (95% CI)
Non-vaccinated	17 801 (73.69)	91 592 (75.84)	1 (ref)	1 (ref)
Vaccinated	6354 (26.31)	29 183 (24.16)	1.16 (1.12 to 1.20)	1.10 (1.06 to 1.15)

*Adjusted only for matching factors (age, sex and calendar year).
†Adjusted for matching factors (age, sex and calendar year) plus the covariates shown in table 1.
ref, reference.

could be overshadowed by the greater background incidence of AMI in this season.

Although several types of bias may account for the reduced risk found associated with vaccination, we cannot rule out the possibility of a biological component different from the prevention of influenza infection. For instance, it has been observed that shortly after vaccination there is an increase in exhaled nitric oxide[25] and a release of interleukin 10 (known to have anti-inflammatory effects) with a reduction of tumour necrosis factor alpha,[26] effects that might reduce the risk of plaque rupture. This short-term anti-inflammatory effect has been demonstrated in an RCT that compared influenza vaccine with a placebo prior to bypass surgery.[27] On the other hand, several studies have shown a long-term protective effect that goes beyond the influenza season.[22 24] In the Influenza Vaccination in Prevention From Acute Coronary Events in Coronary Artery Disease (FLUCAD) study,[28] an RCT theoretically free of most biases, a steady separation of risk curves was observed over 300 days of follow-up. Also, animal studies have shown stabilisation of atheroma plaques for as long as 26 weeks after influenza vaccination.[29] This immunomodulatory effect has also been observed with some types of BCG vaccine.[30]

Key messages

What is already known on this subject?

- Many studies have reported a reduced risk of acute myocardial infarction (AMI) associated with influenza vaccination, mostly in a secondary prevention setting.
- Such protection is allegedly due to the prevention of the infection.
- If so, we should observe a greater effect during epidemic periods, as compared with pre-epidemic and postepidemic periods.

What might this study add?

- Vaccinated persons presented higher comorbidity and comedication than non-vaccinated persons, introducing some confounding.
- After adjustment for this, vaccination was shown to be associated with a moderate reduced risk of AMI (10%–15%), with no apparent difference between epidemic and non-epidemic periods.
- The pneumococcal vaccine, used as a negative control, was not found to be associated with a reduced risk.

How might this impact on clinical practice?

- Influenza vaccination may have a protective effect on AMI risk in the general population (a primary prevention setting), although an adherent user bias may party explain the results.
- A direct biological effect of the vaccine, different from the prevention of influenza infection, cannot be ruled out.

Our study has several limitations. First, as in any observational study, there may be unmeasured factors (frailty, lack of functionality and adherence, among others) that we were not able to control for. Second, we could not distinguish the type of AMI (type 1 due to plaque rupture and type 2 due to an imbalance between oxygen supply and demand), and the possibility exists that influenza vaccine has a differential effect; for instance, if the vaccine had a greater effect on type 1, this inability to distinguish the type of AMI may have led to a dilution of the protective effect. Third, BIFAP only records the vaccinations made through the National Health System, so some vaccinees may have been classified as unexposed if they received the vaccine through a private physician; however, due to the universal coverage of the Spanish public health system and the gratuity of the vaccine, this should be a negligible proportion (in particular among the seniors).

CONCLUSIONS

The results found in the present study are compatible with a moderate protective effect of influenza vaccine on AMI in the general population (mostly in a primary prevention scenario). We have not found differences in the relative risks across epidemic periods, so both bias and the existence of a direct effect of vaccine independent of influenza protection are possible. Further studies addressing the mechanisms by which influenza vaccination is associated with a reduction in CV events are needed.

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