Influenza vaccination, pneumococcal vaccination and risk of acute myocardial infarction: matched case–control study

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**Abstract**

**Background:** Previous studies have shown an association between acute myocardial infarction and preceding respiratory infection. Contradictory evidence exists on the influence of influenza vaccination and pneumococcal vaccination in preventing cardiovascular disease. We aimed to investigate the possible association of influenza vaccination and pneumococcal vaccination with acute myocardial infarction.

**Methods:** We used a matched case–control design with data from the United Kingdom General Practice Research Database. Cases were patients who were at least 40 years of age at diagnosis of first acute myocardial infarction recorded from Nov.1, 2001, to May 31, 2007, and were matched for sex, general practice, age and calendar time (i.e., month corresponding to index date of acute myocardial infarction), with up to four controls each. Data were analyzed using conditional logistic regression, adjusted for vaccination target groups, cardiovascular risk factors, treatment medications and attendances at a general practice.

**Results:** We included 78 706 patients, of whom 16 012 were cases and 62 694 were matched controls. Influenza vaccination had been received in the previous year by 8472 cases (52.9%) and 32 081 controls (51.2%) and was associated with a 19% reduction in the rate of acute myocardial infarction (adjusted odds ratio [OR] 0.81, 95% confidence interval [CI] 0.77–0.85). Early seasonal influenza vaccination was associated with a lower rate of acute myocardial infarction (adjusted OR 0.79, 95% CI 0.75–0.83) than vaccination after mid-November (adjusted OR 0.88, 95% CI 0.79–0.97). Pneumococcal vaccination was not associated with a reduction in the rate of acute myocardial infarction (adjusted OR 0.96, 95% CI 0.91–1.02).

**Interpretation:** Influenza vaccination but not pneumococcal vaccination is associated with a reduced rate of first acute myocardial infarction. This association and the potential benefit of early seasonal vaccination need to be considered in future experimental studies.

Winter peaks in incidence of acute myocardial infarction have been linked to climate,1 metabolic factors2 and infection.3 Because known risk factors do not fully account for cases of acute myocardial infarction, current interest is focused on the putative link with respiratory infection. Significant increases in acute myocardial infarction occur during peak winter incidence of pneumonia, influenza and influenza-like syndrome,4 particularly during years dominated by epidemic rather than nonepidemic influenza A. This association supports the notion that the increase is caused by influenza rather than cold weather.5

Acute myocardial infarction may increase susceptibility to respiratory illness,6 but the association between acute myocardial infarction and respiratory infection occurring within four weeks prior to the acute myocardial infarction7,8 supports infection as a cause of acute myocardial infarction. Although the exact mechanism is unknown, the favoured hypothesis is that infection triggers plaque rupture.9 Although several observational studies, as well as two randomized controlled trials,10,11 suggest a positive effect of influenza vaccine in preventing acute myocardial infarction, they provide insufficient and conflicting evidence.12

The aim of this study was to investigate a possible association between influenza or pneumococcal vaccination and acute myocardial infarction.

**Methods**

**Study design and ethics approval**

We used a matched case–control design study. Each case of acute myocardial infarction was matched to four controls according to age, sex, general practice, age and calendar time (i.e., month corresponding to index date of acute myocardial infarction), using incidence density sampling according to person-time at risk.13 The study was approved by the Independent Scientific Advisory Committee of the General Practice Research Database and the United Kingdom National Research Ethics Service.

**Data sources**

Data were extracted from the General Practice Research Database, an extensively validated computerized database, representative of and comprising 5% of the population of England and Wales.14 Virtually all patients in the database are...
registered with a general practitioner, and all health care attendances are recorded in the database. The database contains reliable, anonymized patient data that includes demographic information, diagnoses, medication, health-related behaviours, referrals and treatment outcomes.

We estimated that 6176 cases and 24 704 controls would provide 90% power to detect an odds ratio (OR) of 0.9 using a two-sided 5% significance level, assuming 70% of controls were vaccinated and with a correlation coefficient of 0.2 between cases and matched controls for a clinically important effect based on current vaccination rates. All available cases in the General Practice Research Database were included in the study.

Selection of cases and controls
Case patients were at least 40 years of age at the time of diagnosis of first acute myocardial infarction (fatal or nonfatal) who had clinical records for over five and a half years (between Nov. 1, 2001, to May 31, 2007) and were identified using standardized (Read and Oxford Medical Information Systems [OXMIS]) codes. The date of acute myocardial infarction, referred to as the index date, was used to match controls. Four controls were selected at random from the eligible matched controls for each case (i.e., before exposure status was known). We included only cases and controls with clinical records for at least five years before the index date to ensure completeness of recording of exposures and confounding variables.

Identification of vaccination status
Only data on influenza and pneumococcal vaccinations administered before the index date were extracted. For the main analyses, influenza vaccination was defined as vaccination given in the year preceding the index date. Other exposures to influenza vaccination considered were influenza vaccination within the current vaccination season (i.e., the same vaccination season as the index date) and early (i.e., between Sept. 1 and Nov. 15) or late vaccination (i.e., between Nov. 16 and Feb. 28 or 29, depending on the year).

Patients were considered to have had a pneumococcal vaccination if they had ever received the pneumococcal vaccine before the index date. Combined vaccination was defined as pneumococcal vaccination ever combined with influenza vaccination in the year preceding the index date.

Confounding variables
Data on potential confounding variables were extracted using Read and OXMIS codes recorded before the index date (Table 1). High-risk categories and target groups are identical for pneumococcal and influenza vaccination, as defined by the UK Department of Health (2008).

Statistical analysis
Conditional logistic regression was used to estimate unadjusted and adjusted ORs and 95% confidence intervals (CIs) for the association between acute myocardial infarction and influenza and pneumococcal vaccination. Since we used incident patient cases who were matched with controls, were free of disease at the end of the study period and were from a dynamic population, ORs were taken as estimating rate ratios. The adjusted analyses accounted for confounders, including target groups for vaccination, additional cardiovascular risk factors, treatments and general practitioner consultations in the preceding five years, grouped into four categories based on quartiles of the distribution (≤ 12, 13–26, 27–44, and ≥ 45). Smoking status was known for most patients (92%) and included in the main analyses; patients whose smoking status was unknown were excluded. Each type of vaccination was adjusted for the other type.

Trends were established using likelihood ratio tests for trend. Subgroup analyses using likelihood ratio tests for interaction were conducted for age (< 65 and ≥ 65 years) and vaccination target group (at least one target group present).

Systolic blood pressure, body mass index (BMI) and total cholesterol were not included in the main adjusted analyses owing to missing data (63%, 45% and 15% completeness respectively). To replace missing values for smoking status, systolic blood pressure, BMI and total cholesterol, multiple imputation was conducted as an additional analysis, creating ten imputed data sets with results combined using Rubin’s rules to account for uncertainty in the imputed data.

Results
We included 16 012 cases and 62 964 matched controls from 379 practices. Most cases (95.7%) had four controls. Confounding factors, apart from splenectomy and chronic liver disease, were reported more frequently in cases than controls (Table 1).

People with risk factors for acute myocardial infarction were more likely to be vaccinated (Table 2), which was expected since many cardiovascular risk factors are also indications for vaccination.

Influenza vaccination and acute myocardial infarction
Uptake of the influenza vaccine and results of the conditional logistic regression are shown in Table 3. The unadjusted analyses showed a slightly increased risk of acute myocardial infarction in vaccinated people. However, this analysis does not account for the fact that vaccinated people make up a preselected group and are already at increased risk for acute myocardial infarction because of their risk factors (unadjusted OR for acute myocardial infarction among people in a high-risk group is 2.26 (95% CI 2.18 to 2.35).

After adjusting for confounding variables, so that vaccinated and unvaccinated groups were comparable in terms of risk factors in the model, we found that influenza vaccination within the previous year was associated with a significantly reduced rate of acute myocardial infarction (adjusted OR 0.81, 95% CI 0.77 to 0.85, \( p < 0.001 \)).

The confounders that contributed most to the change in OR for influenza vaccination were consultation rate, previous coronary heart disease and diabetes mellitus. Number of consultations before acute myocardial infarction was a key variable in the adjusted analysis; patients with more consultations were more likely to receive vaccination, but were also at increased risk of acute myocardial infarction — presumably...
Table 1: Characteristics of cases and controls

| Characteristic                                      | Cases  |
|-----------------------------------------------------|--------|
|                                                     | n = 16 012 | Controls n = 62 694 | Unadjusted OR (95% CI) |
| **Matching variables**                              |        |                    |
| Age, yr                                             |        |                    |
| 40–64                                               | 5 341 (33.4) | 21 359 (34.1) | NA†                |
| ≥ 65                                                | 10 671 (66.6) | 41 335 (65.9) | NA†                |
| Sex                                                 |        |                    |
| Male                                                | 6 168 (38.5) | 24 171 (38.5) | NA†                |
| Female                                              | 9 844 (61.5) | 38 523 (61.5) | NA†                |
| **Vaccination target groups**                       |        |                    |
| Asthma or COPD attack, ever                         | 1 980 (12.4) | 5 803 (9.3) | 1.39 (1.32–1.47) |
| Chronic heart disease                               | 3 756 (23.5) | 6 174 (9.9) | 2.97 (2.83–3.11) |
| Stroke or transient ischemic attack                 | 1 434 (9.0) | 3 487 (5.6) | 1.66 (1.56–1.78) |
| Diabetes                                            | 2 451 (15.3) | 5 637 (9.0) | 1.85 (1.76–1.95) |
| Splenectomy                                         | 36 (0.2) | 116 (0.2) | 1.24 (0.85–1.80) |
| Chronic liver disease                               | 30 (0.2) | 93 (0.2) | 1.26 (0.83–1.90) |
| Chronic renal disease                               | 584 (3.7) | 724 (1.2) | 3.30 (2.94–3.69) |
| Immunosuppression or HIV                            | 2 (0.01) | 3 (< 0.01) | 2.67 (0.45–15.96) |
| **Other cardiovascular risk factors**               |        |                    |
| Hyperlipidemia                                      | 2 180 (13.6) | 5 835 (9.3) | 1.61 (1.52–1.70) |
| Family history of myocardial infarction             | 302 (1.9) | 954 (1.5) | 1.29 (1.12–1.48) |
| BMI recorded within past 3 yr                       | 8 072 (50.4) | 27 434 (43.8) |                    |
| BMI kg/m², mean (SD)                                | 27.3 (5.2) | 27.0 (4.9) | 1.11† (1.04–1.17) |
| Peripheral vascular disease                         | 1 216 (7.6) | 2 084 (3.3) | 2.42 (2.25–2.61) |
| Hypertension                                        | 6 211 (38.8) | 19 538 (31.2) | 1.45 (1.40–1.51) |
| Smoking history                                     |        |                    |
| Never smoked                                        | 6 292 (39.3) | 31 000 (49.4) | 1.00                |
| Ex-smoker                                           | 4 543 (28.4) | 1 545 (25.1) | 1.49 (1.42–1.56) |
| Current smoker                                      | 4 265 (26.7) | 10 263 (16.4) | 2.22 (2.12–2.33) |
| Not recorded                                        | 912 (5.7) | 5 686 (9.1) |                    |
| Systolic blood pressure recorded in past yr         | 11 945 (74.6) | 37 338 (59.6) |                    |
| Systolic blood pressure mmHg, mean (SD)             | 140.5 (21.4) | 141.4 (18.0) | 0.984 (0.96–0.99) |
| Total cholesterol recorded                          | 2 823 (17.6) | 9 150 (14.6) |                    |
| Total cholesterol mmol/L, mean (SD)                 | 5.37 (1.27) | 5.28 (1.13) | 1.04§ (1.00–1.09) |
| **Treatments**                                      |        |                    |
| Treatment with ASA (≥ 2 prescriptions in previous 6 mo) | 1 892 (11.8) | 5 211 (8.3) | 1.52 (1.44–1.62) |
| Treatment with statins (≥ 1 prescriptions in previous yr) | 1 817 (11.4) | 4 372 (7.0) | 1.79 (1.69–1.90) |
| Treatment with antihypertensives (≥ 1 prescriptions in previous yr) | 1 032 (6.5) | 2 468 (3.9) | 1.72 (1.59–1.85) |
| **No. of GP consultations in last 5 yr**            |        |                    |
| ≤ 12                                                | 3 031 (18.9) | 17 196 (27.4) | 1.00                |
| 13–26                                               | 3 749 (23.4) | 16 618 (26.5) | 1.37 (1.30–1.45) |
| 27–44                                               | 4 193 (26.2) | 15 061 (24.0) | 1.79 (1.69–1.89) |
| ≥ 45                                                | 5 039 (31.5) | 13 819 (22.1) | 2.48 (2.34–2.63) |

Note: ASA = acetylsalicylic acid, BMI = body mass index, CI = confidence interval, COPD = chronic obstructive pulmonary disease, GP = general practitioner, NA = not applicable, OR = odds ratio, SD = standard deviation.

*Unless otherwise indicated.
†Variables that were matched and hence not applicable.
‡Per 10-unit increase.
§Per unit increase.
because they were sicker and hence consulting physicians more often. Adjusting for consultation rate alone resulted in an OR for vaccination of 0.84 (95% CI 0.80 to 0.88). However, when we adjusted for all other confounders except consultations, influenza vaccination was still protective (OR 0.87, 95% CI 0.83 to 0.91).

When the association between acute myocardial infarction and influenza vaccination in the last year was further adjusted for “ever receiving pneumococcal vaccination,” the result was an adjusted OR of 0.82 (95% CI 0.78 to 0.86). Vaccination within the current vaccination season was also associated with a significantly reduced rate of acute myocardial infarction (adjusted OR 0.80, 95% CI 0.76 to 0.84, p < 0.001). Most vaccinations administered were given early, between September and mid-November (90.3% in cases and 91.0% in controls). When compared with no vaccination, early vaccination was associated with a 21% reduction in the rate of acute myocardial infarction, whereas late vaccination was associated with a significantly reduced rate of acute myocardial infarction when the last vaccination was given more than a year before the index date.

Repeated vaccination (i.e., vaccination in all previous five or six consecutive seasons) was associated with a significant reduction in the rate of acute myocardial infarction (adjusted OR 0.79, 95% CI 0.74 to 0.84) compared with no vaccinations in the previous five years, as was vaccination within the current season (OR 0.85, 95% CI 0.80 to 0.90), but not consecutively in the five or six preceding vaccination seasons.

We conducted separate analyses and tests for interaction according to vaccination target group (i.e., with at least one target group present). The association between influenza vaccination and acute myocardial infarction was more marked for those in a vaccination target group (adjusted OR 0.70, 95% CI 0.64 to 0.77) compared with those not in a target group (adjusted OR 0.85, 95% CI 0.79 to 0.91, test for interaction p < 0.001).

In the analyses using multiply imputed data with BMI, systolic blood pressure and total cholesterol added to the covariates, the adjusted OR for influenza vaccination in the previous year was 0.83 (95% CI 0.80 to 0.88).

**Pneumococcal vaccination and acute myocardial infarction**

Just over one-third of cases (35.4%) and controls (34.7%) had been vaccinated within 10 years of the index date. Of all those who reported pneumococcal vaccination, 27,257 of 27,887 had received a pneumococcal vaccination before the index date (Appendix 1, available at www.cmaj.ca/cgi/content/full/cmaj.091891/DC1), and almost all of these (27,257 of 27,887) had been vaccinated within 10 years of the index date.

**Table 2: Distribution of risk factors for acute myocardial infarction by vaccination**

| Risk factor                        | No vaccination n = 35,244 | Influenza vaccination only n = 15,575 | Pneumococcal vaccination only n = 2,909 | Combined vaccination n = 24,978 |
|------------------------------------|---------------------------|--------------------------------------|----------------------------------------|-------------------------------|
| Chronic heart disease              | 2,026 (5.8)               | 2,111 (13.6)                         | 586 (20.1)                             | 5,207 (20.9)                 |
| Stroke or TIA                      | 1,103 (3.1)               | 1,150 (7.4)                          | 268 (9.2)                              | 2,400 (9.6)                 |
| Diabetes                           | 1,392 (4.0)               | 1,430 (9.2)                          | 561 (19.3)                             | 4,705 (18.8)                |
| Asthma or COPD                     | 1,583 (4.5)               | 1,466 (9.4)                          | 500 (17.2)                             | 4,234 (17.0)                |
| Chronic liver disease              | 43 (0.1)                  | 25 (0.2)                             | 12 (0.4)                               | 43 (0.2)                    |
| Chronic renal disease              | 240 (0.7)                 | 245 (1.6)                            | 118 (4.1)                              | 705 (2.8)                   |
| Splenectomy                        | 22 (0.1)                  | 3 (0.02)                             | 30 (1.0)                               | 97 (0.4)                    |
| Hypertension                       | 7,345 (20.8)              | 5,822 (37.4)                         | 1,203 (41.4)                           | 11,379 (45.6)              |
| Peripheral vascular disease        | 824 (2.3)                 | 680 (4.4)                            | 173 (6.0)                              | 1,623 (6.5)                 |
| Hyperlipidemia                     | 2,358 (6.7)               | 1,605 (10.3)                         | 366 (12.6)                             | 3,686 (14.8)                |
| Current smoker                     | 8,671 (28.6)              | 2,438 (16.7)                         | 480 (17.2)                             | 2,939 (12.1)                |
| Obesity or overweight              | 7,900 (22.4)              | 4,595 (29.5)                         | 999 (34.3)                             | 9,689 (38.8)                |
| Treatment with antithrombin         | 949 (2.7)                 | 672 (4.3)                            | 173 (6.0)                              | 1,706 (6.8)                 |
| Treatment with statins             | 1,486 (4.2)               | 1,263 (8.1)                          | 319 (11.0)                             | 3,121 (12.5)                |
| Treatment with ASA                 | 1,601 (4.5)               | 1,458 (9.4)                          | 350 (12.0)                             | 3,694 (14.8)                |
| Family history of AMI              | 531 (1.5)                 | 261 (1.7)                            | 43 (1.5)                               | 421 (1.7)                   |
| Average no. GP consultations in the past 5 yr, mean (95% CI) | 19.3 (19.1–19.5) | 36.3 (35.9–36.7) | 41.1 (40.0–42.2) | 44.9 (44.6–45.3) |

Note: AMI = acute myocardial infarction, ASA = acetylsalicylic acid, CI = confidence interval, COPD = chronic obstructive pulmonary disease, GP = general practitioner, TIA = transient ischemic attack.

*Unless otherwise indicated.
When adjusted for all covariates including influenza vaccination, there was no significant effect of pneumococcal vaccination (adjusted OR 0.96, 95% CI 0.91 to 1.02). Using multiply imputed data and also adjusting for BMI, systolic blood pressure and total cholesterol, the adjusted OR for pneumococcal vaccination was 0.98 (95% CI 0.93 to 1.04). Combined influenza and pneumococcal vaccination did not show significant benefit when compared with influenza vaccination alone (adjusted OR 0.94, 95% CI 0.89 to 1.01, \( p = 0.07 \)).

**Interpretation**

Influenza vaccination within the past year was associated with a 19% reduction in the rate of acute myocardial infarction or its complications. Previous observational studies have been limited by methodologic issues such as recall bias, misclassification of exposure and outcome, and time-varying confounders. Our findings provide evidence from observational studies of primary prevention suggesting a beneficial effect of influenza vaccination for prevention of acute myocardial infarction compared with no vaccination. Pneumococcal vaccination or combined vaccination had no additional benefit compared with influenza vaccination alone.

Unsurprisingly, cases and controls were different in their disease and treatment characteristics, with cases more likely to have comorbidities or be receiving treatment than controls. Cases were more likely to have been vaccinated than controls, particularly those between age 40 and 64 years, a finding that accords with current UK guidelines to vaccinate all those in a target group. Importantly, we found that multivariate adjustment for confounding factors led to a protective association for influenza vaccination.

Convincing evidence of a protective role for influenza infection is emerging. Our findings lend support to previous evidence from observational studies of primary prevention and randomized studies of secondary prevention suggesting a beneficial effect of influenza vaccination for prevention of acute myocardial infarction or its complications. Previous observational studies have been limited by methodologic problems, including recall bias in self-reported vaccination history.

**Table 3:** Association between influenza vaccination and acute myocardial infarction

| Characteristic                                      | No. (%) | Unadjusted | Adjusted* | Multiply imputed data, adjusted† |
|-----------------------------------------------------|---------|------------|-----------|----------------------------------|
| **Vaccination in preceding yr**                     |         |            |           |                                  |
| All ages (≥ 40 yr)                                  | 16 012  | 1.00       | 1.00      | 1.00 (0.78–0.90)                 |
| < 65 yr                                             | 3 015   | 1.11       | 1.07      | 1.07 (0.98–1.17)                 |
| ≥ 65 yr                                            | 7 437   | 1.13       | 1.07      | 1.07 (0.98–1.17)                 |
| **Time since last vaccination at index date, mo**   |         |            |           |                                  |
| Never vaccinated                                    | 5 842   | 1.00       | 1.00      | 1.00 (0.78–0.90)                 |
| 0–3                                                 | 3 187   | 1.16       | 1.07      | 1.07 (0.98–1.17)                 |
| 3–6                                                 | 2 230   | 1.22       | 1.13      | 1.13 (1.05–1.21)                 |
| 6–12                                                | 3 055   | 1.27       | 1.19      | 1.19 (1.12–1.26)                 |
| 12–60                                               | 1 447   | 1.55       | 1.45      | 1.45 (1.38–1.53)                 |
| ≥ 60                                                | 251     | 1.21       | 1.05      | 1.05 (0.89–1.21)                 |
| **Within-season vaccination**                       |         |            |           |                                  |
| Yes                                                 | 7 496   | 1.07       | 1.02      | 1.02 (0.96–1.08)                 |
| Early within-season (Sept. to mid-Nov.)             | 6 770   | 1.07       | 1.01      | 1.01 (0.96–1.06)                 |
| Late within-season (mid-Nov. to Feb.)               | 726     | 1.16       | 1.05      | 1.05 (0.99–1.11)                 |
| **Vaccination in previous yr, by mo of index date** |         |            |           |                                  |
| Sept. to Nov.                                       | 1 744   | 0.97       | 0.89      | 0.89 (0.83–0.95)                 |
| Dec. to Mar.                                        | 3 418   | 1.13       | 1.06      | 1.06 (0.99–1.13)                 |
| Apr. to Aug.                                        | 3 310   | 1.11       | 1.03      | 1.03 (0.97–1.07)                 |

Note: CI = confidence interval, OR = odds ratio.

*Adjusted for asthma or chronic obstructive pulmonary disease, chronic heart disease, stroke or transient ischemic attack, diabetes, splenectomy, chronic liver disease, chronic renal failure, immunosuppression and HIV, hyperlipidemia, family history of acute myocardial infarction, peripheral vascular disease, hypertension, smoking status, treatment with acetylsalicylic acid, treatment with statins, treatment with antihypertensives, and general practice consultations.

†Adjusted for all of the above variables as well as for body mass index, systolic blood pressure and total cholesterol using 10 multiply imputed data sets.

*Totals for the period of Sept. to Nov. were 3723 cases and 14 599 controls. Totals for the period of Dec. to Mar. were 6146 cases and 24 036 controls. Totals for the period of Apr. to Aug. were 6143 cases and 24 059 controls.
Research

Studies with no evidence of benefit had low power, poor case ascertainment, misclassification of vaccination status and lack of investigator blinding. The additional benefit of early within-season influenza vaccination (i.e., during the period from September to mid-November) compared with late vaccination (i.e., after mid-November) has been suggested by findings of previous research, but is not part of current recommendations for influenza vaccination.

Given that influenza vaccination is likely to be effective only against circulating strains of influenza virus, our findings are strengthened by the biological plausibility of a within-season or within-year effect of influenza vaccination in preventing influenza-related acute myocardial infarction. The finding that influenza vaccination was associated with a reduction in the risk of acute myocardial infarction, whereas no effect was found for pneumococcal vaccination, is evidence against the explanation that unknown confounders constituted a “healthy user” effect. If the 12-month protective effect of influenza vaccination was a result of confounding by indication, then we would also expect to find a protective effect for influenza vaccination beyond 12 months and for pneumococcal vaccination by the same token. But we did not. We believe that this discrepancy also supports the plausibility of our findings, and that the difference between the effect of early versus late vaccination on the risk of acute myocardial infarction cannot be explained by confounding by indication. Influenza vaccination was beneficial regardless of the month of acute myocardial infarction. This finding could be an indication of longer-term benefits for prevention of influenza infection, given that vaccinations considered in this instance had been given in the preceding 12 months. Following biological explanations for the association between acute myocardial infarction and influenza, the flu virus would have had a lesser effect on the vaccinated patients’ circulatory systems.

Although previous studies have shown an additive effect of pneumococcal vaccination for prevention of respiratory disease, we did not find a reduction in the rate of acute myocardial infarction for pneumococcal vaccination after adjusting for influenza vaccination, even among people aged 65 years and over. Our findings contrast with those of a recent study suggesting that pneumococcal vaccination was associated with a 50% reduction in the rate of acute myocardial infarction. Investigators in that study did not account for differences in cardiovascular risk factors, nor, crucially, for the confounding effect of influenza vaccination.

Strengths and limitations

Despite their known problems of bias and confounding, case-control designs are efficient in examining the association between outcomes and exposures. The large General Practice Research Database sample provided good power to investigate associations in a representative population with precision. We minimized selection bias by including all cases of acute myocardial infarction within the selected time period and matched controls, free of the outcome of interest and independent of the exposure of interest. Matching for age, sex, practice and calendar time (month corresponding to index date of acute myocardial infarction) increased the precision of our results compared with those of previous, unmatched case-control studies. Information on exposures was recorded before the index date, eliminating recall bias.

To minimize bias due to misclassification and missing data, patients were selected only if they had at least five years of up-to-standard data on the General Practice Research Database. To reduce confounding from “healthy user,” “indication” or “treatment” biases, we adjusted for many known confounders, including vaccination target groups and cardiovascular risk groups, treatments and general practitioner consultation rate, of which the latter is thought to be related to functional and economic status. Potential confounders such as functional status were not fully accounted for because of unavailability of data, and we did not have data for other triggers, such as stressful life events. Although we observed missing values for variables such as smoking status, systolic blood pressure, BMI and total cholesterol, we used standard imputation procedures to account for these and obtained results similar to those of our complete case analysis.

Conclusion

Our findings reinforce current recommendations for annual influenza vaccination of target groups, with a potential added benefit for prevention of acute myocardial infarction in those without established cardiovascular disease. This benefit may lead to an increase in suboptimal rates of vaccination, particularly among younger patients.

Further research is needed to confirm our finding that early vaccination, in particular, confers additional reduction in risk for acute myocardial infarction. If substantiated, this finding has implications for timely supply and administration of influenza vaccine and could lead to changes in recommendations for timing of vaccination.

This article has been peer reviewed.

Competing interests: None declared.

Contributors: Niroshan Siriwardena had the initial idea for the study and received support in the conception and design of the study from Carol Coupland. Stella Gwini was involved in the design of the study, performed the analysis of the data supported by Carol Coupland, and wrote the first draft of the article. All of the authors interpreted the results, participated in reviewing and revising the manuscript, and approved the final version of the manuscript submitted for publication.

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