Association of Influenza Vaccination and Reduced Risk of Recurrent Myocardial Infarction

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Background—Numerous studies have suggested that microbial agents may promote atherosclerosis. A smaller body of research has suggested that acute respiratory infection may be a risk factor for myocardial infarction (MI). We hypothesized that influenza vaccine might reduce the risk of recurrent MI in patients with documented coronary heart disease (CHD).

Methods and Results—A case-control study was performed on 218 CHD patients seen at Memorial Hermann Hospital during the influenza season of October 1997 through March 1998. Patients who experienced new MI were included in the case group, and those who did not experience new MI or unstable angina were assigned to the control group. Data were collected by structured review of patients’ charts and through a subsequent telephone survey. Adjusted for history of influenza vaccination in previous years, multivariate logistic regression revealed risk of MI to be associated with current hypertension (OR 4.96, 95% CI 2.06 to 11.96, \( P \leq 0.0001 \)), hypercholesterolemia (OR 4.08, 95% CI 1.67 to 9.99, \( P \leq 0.002 \)), smoking (OR 3.75, 95% CI 1.76 to 7.98, \( P \leq 0.001 \)), and influenza vaccination (OR 0.33, 95% CI 0.13 to 0.82, \( P \leq 0.017 \)). Despite significant association in univariate analysis, multivitamin therapy and physical exercise were not associated with risk of reinfarction in multivariate analysis.

Conclusions—In this study in patients with chronic CHD, vaccination against influenza was negatively associated with the development of new MI during the same influenza season. However, to address causal inference, examination of prospective data sets will be needed. (Circulation. 2000;102:3039-3045.)

Key Words: influenza vaccine ▪ myocardial infarction ▪ prevention ▪ atherosclerosis ▪ infection

It is now widely recognized that abnormal serum lipids, hypertension, smoking, diabetes, physical inactivity, and obesity are modifiable risk factors for coronary heart disease (CHD). These traditional risk factors, however, are not by themselves sufficient to explain the total burden of CHD in populations. Recent studies have implicated an important role for inflammation in development of atherosclerosis. Inflammation may be initiated by oxidized LDL, but there is increasing evidence that infection may play a role in the development of atherosclerosis as well. Several studies have been conducted to elucidate the association of infection with development of atherosclerosis, but few studies have been performed on triggering of acute coronary syndromes by infections. One prospective study and several retrospective studies have suggested that acute respiratory infection might trigger myocardial infarction (MI).

A possible relationship between influenza and MI was first suggested after epidemics of influenza struck Europe and the United States in the early 1900s. In those epidemics, about half of the excess mortality was attributed to causes other than influenza, including heart disease. Influenza vaccine reduces the risk of acquiring influenza and of hospitalization and death, particularly among the elderly. As yet, however, no studies have explored the potential of preventing acute respiratory infections to prevent MI. We therefore hypothesized that influenza vaccination might reduce the incidence of MI in patients with established coronary atherosclerosis.

Methods

Design and Data Collection

We conducted a case-control study among all patients with a previous history of MI who were seen in the University of Texas–Houston outpatient cardiology office during the influenza season of October 1, 1997, to March 31, 1998. Patients who experienced a new MI (International Classification of Diseases [ICD] 10: 410.0 to 410.9, as documented by the treating physician on the basis of having at least 2 of the 3 criteria: ECG, enzymes, and clinical presentation)were included in the case group, and those who did not experience new MI or unstable angina were assigned to the control group. Data were collected by structured review of patients’ charts and through a subsequent telephone survey. Adjusted for history of influenza vaccination in previous years, multivariate logistic regression revealed risk of MI to be associated with current hypertension (OR 4.96, 95% CI 2.06 to 11.96, \( P \leq 0.0001 \)), hypercholesterolemia (OR 4.08, 95% CI 1.67 to 9.99, \( P \leq 0.002 \)), smoking (OR 3.75, 95% CI 1.76 to 7.98, \( P \leq 0.001 \)), and influenza vaccination (OR 0.33, 95% CI 0.13 to 0.82, \( P \leq 0.017 \)).
during the season were included in the case group. The total number of MI patients initially included in the case group was 122. After the case group was studied, a control group was selected by systematic random sampling from those who were seen during the season for their regular follow-up who had not experienced new MI or exacerbation of their disease.

Two physicians reviewed patients’ medical records in a consistent manner and filled out a questionnaire designed for the study. After the chart review, patients were interviewed via telephone about their exposure to influenza vaccine and other relevant questions, including the actions they normally took in response to an upper respiratory infection or influenza. The patients’ medical histories were also confirmed during the interview.

Four of the 122 cases died before the interviews were conducted, and 9 of the cases and 2 of the controls could not be contacted by telephone. Finally, a total of 218 patients (109 cases and 109 controls) were included for analysis. No attempt was made to collect data on patients’ development of influenza, because these kind of data are subject to recall bias, and patients may easily mistake symptoms of other upper respiratory tract infections for influenza.

Data Analysis
We compared frequency of each factor in the case and control groups in contingency tables by calculating $\chi^2$, using Yates’ correction. For nonnormally distributed variables, a Mann-Whitney nonparametric test was used.

To adjust for effects of the background factors and to calculate the OR of new MI for each independent factor, a multiple logistic regression model was fitted with a forward stepwise algorithm. Parameter estimation was done by the likelihood ratio method, and probabilities for removal and entry of factors were set to 0.10 and 0.05, respectively. A constant term was included in the model, and so may help correct for confounding by socioeconomic factors (see Discussion).

Multivariate Predictors of Vaccination
To explore the characteristics of patients who received influenza vaccine, we developed a multivariate analysis. In a logistic regression model tested to find factors independently associated with vaccination (Table 3), we found those with a history of receiving the vaccine in most prior years were 21 times more likely and those older than 60 years were 5 times more likely to get the influenza vaccine. Other variables (namely, history of CHD risk factors, current hypertension, and hypercholesterolemia), medications, and treatment history were not significantly different between the vaccinated and unvaccinated groups (Table 3).

Variables Associated With MI
The Figure shows the results of logistic regression analysis. Variables with an arbitrarily defined $P$ value $< 0.1$ in univariate analysis (Table 1) were selected for entry into the model. We then used a forward stepwise method to find the most important factors associated with the development of new MI. However, we forced vaccination history to remain in the model as a marker of health-conscious behavior (see Discussion).

Among the 8 factors of Table 1 that met the above criteria ($P<0.1$), 4 remained significant in the final model: current hypertension (OR 4.96, 95% CI 2.06 to 11.96, $P<0.0001$), current hypercholesterolemia (OR 4.08, 95% CI 1.67 to 9.99, $P=0.002$), current smoking (OR 3.75, 95% CI 1.76 to 7.98, $P=0.001$), and influenza vaccination in the current season (OR 0.33, 95% CI 0.13 to 0.82, $P=0.017$). For multivitamin therapy, exercise, and treatment after influenza, the significance level dropped in the presence of the other factors, so these factors were omitted from the model. The model had a goodness of fit of 177.16 and a $\chi^2$ equal to 60.25 ($P<0.00005$).

We considered the possibility that influenza vaccination was merely a marker for identifying patients who were at low risk because of other, unmeasured factors. Examples might include better diets, less stress, or socioeconomic variables such as education. In addition to controlling for multivitamin use and exercise (behaviors associated with education and health consciousness), we forced the model to include a history of vaccination in most or all prior years (as opposed to the current influenza season). As shown in the Figure, vaccination in the current year remained strongly associated with freedom from MI (OR 0.33, 95% CI 0.13 to 0.82, $P=0.017$).

Discussion
In this case-control study of 233 patients with a prior MI, adjusted for other predictive variables, vaccination against influenza was associated with an average reduction of 67% (95% CI 18% to 87%) in the risk of subsequent MI. Although in our univariate comparison of 19 factors, 8 entered into the logistic regression model, only 4 remained statistically meaningful by the forward stepwise method. To the best of our knowledge, this is the first report of an association of influenza vaccination with reduced risk of subsequent MI.
Because of its nature, the present study was not able to determine an association of influenza vaccine with fatal MI. The loss to contact by telephone was quite small. The possibility of diagnostic misclassification (eg, misdiagnosing influenza myocarditis as MI) is unlikely because the diagnosis of MI required characteristic angina and typical evolution of cardiac enzymes, as well as ECG changes in contiguous

Study Limitations

Because of its nature, the present study was not able to determine an association of influenza vaccine with fatal MI. The loss to contact by telephone was quite small. The possibility of diagnostic misclassification (eg, misdiagnosing influenza myocarditis as MI) is unlikely because the diagnosis of MI required characteristic angina and typical evolution of cardiac enzymes, as well as ECG changes in contiguous
leads. However, influenza is an uncommon cause of myocarditis, which in turn is an uncommon disease compared with MI in patients with known CHD.

A recall bias is also possible, although not likely, because only 2.8% of cases and 5.5% of controls were unable to remember if they had been vaccinated \( (P=0.49) \). However, some of the patients may have confused influenza with other acute upper respiratory infection.

Therapeutic bias is another possibility, even though the vaccinated and unvaccinated groups were similar in terms of major risk factors. If doctors tended to prescribe the influenza vaccine to patients who were sicker in ways that were not measured in the study (for example, mild dyspnea at rest, history of chronic bronchitis, or diminished forced vital capacity), or if sicker patients tended to request the influenza vaccine more than patients who felt well, then sicker patients would have been overrepresented in the group that received the vaccine, and this would cause the protection by influenza vaccine to have been underestimated. Alternatively, if as previously reported, those who had requested influenza vaccine were better educated or more motivated to preserve their health,\(^\text{15}\) then this would have caused influenza vaccine to be spuriously associated with protection. The rationale for this is that high educational and/or socioeconomic attainment has an independent association with longevity.\(^\text{16}\) In fact, in our patients, the only factors associated with being vaccinated for the current influenza season were age and prior history of vaccination, not illness (Table 3).

In the univariate analysis, a history of receiving influenza vaccinations in most prior years was associated with protection against reinfarction. Thus, the habit of receiving the influenza vaccine may be a marker for education, adherence, motivation, or quality of health care (or, alternatively, for illness). However, when entered in the multiple logistic regression model for prediction of MI, prior vaccination did not appear to be significant (OR 1.25, 95% CI 0.45 to 3.43, \( P=0.67 \)). Likewise, the use of multivitamins (another possible marker of health consciousness and socioeconomic status) was not significantly associated with reduced risk of MI. The same was true for regular physical exercise, which has been associated with education and health consciousness: exercise was not associated with the reduced risk of reinfarction. Thus, it is not likely that vaccination against influenza is associated with a reduced risk of new MI simply because vaccinated patients are more health conscious.

Moreover, even if there were residual confounding, it is not likely that socioeconomic or psychological factors or adherence could account for an apparent 67% reduction in risk. Indeed, the inverse might also be considered: vaccination, multivitamin therapy, exercise, and other such health aids may well be mechanisms that mediate the superior health outcomes of patients who are educated and health conscious or whose doctors are knowledgeable and conscientious.

Additional potential confounding factors include patient behaviors when struck with influenza. Behaviors and physiological responses likely to decrease the risk of MI during influenza (thereby overestimating the importance of influenza vaccination as a preventive strategy) include rest, diminished intake of foods (including foods high in glucose and fats), cessation of cigarette smoking, a fall in blood pressure, and an increased use of aspirin. On the other hand, patients may take large amounts of nonsteroidal anti-inflammatory drugs or decongestants, which raise their blood pressure and put them at higher risk of MI. Our data on self-administered therapies are not detailed enough to clarify this issue.

Another consideration could be a possible difference between the cases and controls with respect to medical treatments that are not measured in this study, such as \( \beta \)-blockers, ACE inhibitors, and other drugs that have been shown to

| TABLE 2. Frequency of Current Season Vaccination by Vaccination History |
|---------------------------------|---------------|---------------|-----------|
| History of Receiving Influenza Vaccine | CHD Patients With New MI (Cases; \( n=109 \)) | CHD Patients Without New MI ( Controls; \( n=109 \)) | \( P^* \) |
| Every year or some years | | | |
| Vaccine in current season | | | |
| Yes | 50 (72%) | 66 (82%) | 0.203 |
| No | 19 | 14 | | |
| Never | | | |
| Vaccine in current season | | | |
| Yes | 0 (0%) | 7 (30%) | 0.002 |
| No | 37 | 16 | | |

*Two-sided asymptotic significance for \( \chi^2 \) with continuity correction.
†Three patients could not recall whether they received the influenza vaccine in the current season.
‡Six patients could not recall whether they received influenza vaccine in the current season.

| TABLE 3. Factors Associated With Influenza Vaccination |
|---------------------------------|-----------------|-----------------|-----------|
| History of receiving influenza vaccine in most prior years | 21.2 | 8.28 | 54.38 | \(<0.00001\) |
| Age<60 | 5.06 | 2.24 | 11.42 | \(<0.00001\) |
| Current hypertension | 0.51 | 0.2 | 1.27 | 0.15 |
| Current hypercholesterolemia | 0.48 | 0.18 | 1.3 | 0.15 |
| Current smoking | 0.8 | 0.37 | 1.8 | 0.56 |

*Multivariate analysis with logistic regression model.
reduce risk of secondary MI. However, both the control and case groups were chosen from the same clinic in a single academic setting (University of Texas-Houston, Memorial Hermann Hospital), where use of aspirin, statins, β-blockers, and ACE inhibitors is nearly uniform (W. Casscells, unpublished survey, 1997).

Finally, because influenza vaccine does not completely protect against influenza, this study may not fully represent the exact amount of risk due to influenza infection.

**Potential Mechanisms**

A case-control study can at best suggest a hypothesis for prospective testing. Whether such studies are worth pursuing depends in part on presence of biological plausibility. The association of influenza vaccination with reduced risk of MI may have biological plausibility as follows:

First, plaque rupture and erosion are common factors precipitating acute coronary events, and inflammation is believed to contribute to plaque rupture. Influenza could, in theory, affect atherosclerotic plaques, causing them to become more inflamed. Interestingly, in a study of 14 patients with coronary aneurysms secondary to inflammation, 10 had histories of an influenza-like syndrome.

A second mechanism might be the triggering of other infections, such as activation of plaque cytomegalovirus or herpes simplex virus, or influenza-mediated decrease in immune response to *Chlamydia pneumoniae*. These pathogens have been hypothesized to contribute to atherosclerosis and perhaps to plaque rupture.

Third, plaques might be activated indirectly by influenza. For example, elevated levels of circulating tumor necrosis factor-α may increase the proliferation and activity of plaque macrophages, and reactive oxygen species might contribute to activation of matrix metalloproteinases.

Fourth, influenza virus infection may cause endothelial dysfunction, as reported for cytomegalovirus and *Chlamydia pneumoniae* infection. Dysfunctional endothelium promotes coronary vasoconstriction and attachment of leukocytes and reduces its anticoagulant and fibrinolytic capacity. Viral infection could also cause endothelial apoptosis, a prothrombotic development.

Fifth, infections in general increase the coagulability of circulating blood via leukocytosis, platelet aggregation, increase in fibrinogen and C-reactive protein, decrease in antithrombin-III, and activation of circulating leukocytes. Influenza has a hemagglutinating activity, and incorporation of influenza virus in human platelets increases platelet aggregation. Antiviral treatment reduces platelet aggregation induced by influenza virus.

Sixth, plasma viscosity as an independent risk factor for MI can be increased during fever, particularly if the patient becomes dehydrated.

A seventh potential factor is the increase in serum glucose and triglycerides in response to an acute infection. Higher serum levels of triglyceride and glucose promote endothelial dysfunction.

An eighth mechanism might be the tachycardia that occurs in response to fever. It has been hypothesized that an increase in heart rate increases the statistical chance that a given cardiac contraction will lead to mechanical rupture of the plaque.

A ninth mechanism might be an increase in psychological stress. Infection may cause one to miss work (reducing income) or to miss some other anticipated activity. Many illnesses can trigger depression or anxiety, which are independent predictors of MI.

**Conclusions**

**Need for Future Studies**

For the reasons described above, a case-control study is not definitive, but it can generate new hypotheses. Fortunately,
Influenza vaccines have been studied in randomized controlled trials, and there are complete, locked data sets that should be available to examine the hypothesis that vaccination reduces the risk of secondary or primary MI in a prospective manner. However, there may be a need for further randomized controlled trials. Such trials could also determine whether there is an early hazard due to a systemic inflammatory response to the vaccine, for example. Data could be collected on the heterogeneity of immune response to influenza vaccine and also to explore the possible noninfluenza-specific effects on general immune responsiveness of the patients with potential protective effects against other infectious agents. Trials could also examine the potential interaction of influenza vaccine with other therapies for coronary artery disease, such as the effects of aspirin, β-blockers, and statins, as well as the effects of patient behavior in response to an attack of influenza, including the possible effects of rest, decongestants, antipyretics, and anti-inflammatory medications.

**Implications**

Our rather small-sample case-control study showed a significant reduction in recurrent MI after influenza vaccination and calls for revalidation of its findings in larger studies with different methodologies. If influenza vaccination protects against MI in patients with chronic coronary atherosclerosis, educating this population (and physicians) could help increase the rate of vaccination, which is still below 65% for those over 65 years of age and/or with chronic heart, lung, or kidney disease (the year 2000 recommendation of the US Centers for Disease Control and Prevention that the age of vaccination be lowered to 55 means the vaccination rate is well below 65%). It will be important to learn whether the vaccination confers protection against fatal MI, cardiac arrest, or stroke or protects those under 55 years of age who have risk factors but no known CHD.

Another interesting question would be the potential of prophylaxis and early treatment of influenza with amantadine or rimantadine, or newer agents (eg, neuraminidase inhibitors), to prevent an MI.

Numerous trials confirm that vaccination prevents influenza, superimposed pneumonia, and mortality. It may be worth exploring whether influenza-triggered MI contributes to the well-documented increase in MIs during the winter months and to the higher rates of MI among the economically and educationally disadvantaged. It will also be interesting to determine whether pneumococcal vaccination, which is even more underutilized than influenza vaccine, protects against MI.

In conclusion, this case-control study suggests that vaccination against influenza may reduce the risk of MI.

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**References**

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