Association Between Influenza Vaccination and Reduced Risk of Brain Infarction

Philippa Lavallée, MD; Véronique Perchaud, MD; Marion Gautier-Bertrand; David Grabli, MD; Pierre Amarenco, MD

Background and Purpose—Because infections subsequent to influenza may play a role in promoting the complications of atherosclerotic disease and may also induce hypercoagulation, we hypothesized that influenza vaccination may protect against brain infarction.

Methods—During the influenza epidemic period we studied 270 subjects, including 90 consecutive patients older than 60 years admitted to the hospital for brain infarction and 180 population-based controls, matched for age, sex, and district of residency in Paris. We conducted a structured interview on whether they had been vaccinated during the last influenza vaccination campaign or every year during the 5 last years.

Results—we found significantly fewer vaccinated subjects during the last vaccination campaign among patients with brain infarction than among controls (46.7% versus 59.4%; \( P = 0.036 \)) and fewer patients vaccinated every year during the last 5 years (41.1% versus 56.1%; \( P = 0.017 \)). After adjustment for age, traditional risk factors, and recent use of antibiotics, the risk of stroke was reduced in the subjects vaccinated during the year of the study and in those vaccinated during the last 5 years, with an odds ratio of 0.50 (95% CI, 0.26 to 0.94; \( P = 0.033 \)) and 0.42 (95% CI, 0.21 to 0.81; \( P = 0.009 \)), respectively. Similar associations were observed in cases and controls free of previous cardiovascular history. Subjects younger than 75 years and subjects free of risk factors or in high social class were significantly less often vaccinated than controls.

Conclusions—Influenza vaccination may protect against brain infarction by reducing infections or may identify a subgroup of patients at low risk for stroke because of a better lifestyle. These results give rise to a new hypothesis for research into stroke prevention. (Stroke. 2002;33:513-518.)

Key Words: cerebral infarction ■ infection ■ influenza vaccine ■ stroke prevention

Acute and chronic infections have been associated with ischemic stroke and myocardial infarction.1–9 These associations were found in young, middle-aged, and elderly subjects, irrespective of ischemic stroke subtype. The infections involved were mainly acute and chronic respiratory tract infections. Epidemiological studies have found a relationship between cardiac and cerebral vascular diseases and inflammation markers, eg, C-reactive protein, as well as infection markers, eg, Chlamydia pneumoniae antibodies.10–22 Chlamydia and herpes virus, as well as inflammation, have been identified in carotid artery plaques.23–27 Subsequent studies suggest that antibiotic treatment may reduce the risk of a recurrent vascular event, although this is still under evaluation.28–32 Thus, infections may play a role in promoting the development of atherosclerotic plaques or in triggering their complications.

Because subjects who are vaccinated against influenza are less prone to viral (influenza) infections and subsequent bacterial infection complications,33 we hypothesized that vaccinated subjects may be at lower risk of brain infarction than nonvaccinated subjects.

Subjects and Methods

Cases

The cases studied were all patients aged 60 years or older, consecutively admitted to our institution for a brain infarction during the winter period corresponding to the influenza epidemic period. They were enrolled in the study between December 1998 and March 1999 and between January and March 2000. Brain infarction was defined as a focal neurological deficit of acute onset lasting >24 hours, with a CT scan or MRI that ruled out an intracranial hemorrhage. Patients reporting a previous cardiovascular or cerebrovascular history were eligible. All patients were examined and interviewed face-to-face during their hospital stay, following a structured questionnaire, by a neurologist (P.L., V.P.).

Controls

The controls were randomly identified from the electoral rolls. Two controls were matched with each case for age (±2 years), sex, and district of residency in Paris. The controls were interviewed by...
Vaccination Questionnaire
The patients and controls were asked whether they had been vaccinated during the preceding influenza vaccination campaign (which takes place in October in France) and whether they had been vaccinated every year during the last 5 years. In the event of aphasia, coma, or somnolence, the closest relative was interviewed. We decided to include patients older than 60 years because they have a higher risk of atherothrombotic stroke than younger patients.

In addition, the subjects were asked whether they had been treated with antibiotics in the previous 3 months and whether they suffered from chronic bronchitis. Chronic bronchitis was defined as the presence of cough and expectoration during at least a 3-month period for at least 2 years.

Data Collection and Definition of Risk Factors
Information on demographic characteristics and risk factors was collected with the use of a structured questionnaire. Hypertension was defined as a history of treated hypertension. Smoking history was coded as never, former smoker (stopped smoking at least 1 year before inclusion in the study), and current smoker. The subjects were classified as diabetics if they were treated for insulin-dependent or non–insulin-dependent diabetes. The patients and controls were asked whether they had ever had a blood cholesterol assay and whether they used a lipid-lowering agent or followed a low-cholesterol diet. A history of myocardial infarction, angioplasty, coronary artery bypass surgery, stroke, or transient ischemic attacks was recorded for both cases and controls; a positive cardiovascular history was defined as the presence of any of these diseases.

We divided the patients and controls into 2 groups according to their job. Employees and blue-collar workers were classified in group 1 (“lower” socioeconomic group) and white-collar workers other than employees in group 2 (“higher” socioeconomic group).

Data Analysis
We compared the frequency of vaccination in the cases and controls using conditional logistic regression analysis for matched sets.64 The odds ratios and 95% CIs were computed. Multivariate analyses were performed to adjust for other variables with the use of a backward selection procedure with 0.10 as the significance level for staying in the model. Since influenza vaccination was reimbursed entirely by the social security system in France for subjects older than 70 years, we conducted age-stratified analyses using 75 years as the cutoff because subjects older than 75 years could have obtained free vaccinations for 5 years. Analyses restricted to cases and controls with no previous cardiovascular or cerebrovascular history are also reported. Statistical testing was performed at the 2-tailed 0.05 level. The data were analyzed with the SAS package.65

Results
The baseline characteristics of the 90 patients and 180 controls are shown in Table 1. As shown in Table 2, patients with brain infarction were less often vaccinated against influenza infection than controls (1) during the preceding vaccination campaign (46.7% versus 59.4%; \( P=0.036 \)) and (2) every year in the previous 5 years (41.1% versus 56.1%; \( P=0.017 \)). After adjustment for the traditional risk factors for stroke and other potential confounding factors, the results remained significant, with an odds ratio of 0.45 (95% CI, 0.24 to 0.84; \( P=0.012 \)) and 0.37 (95% CI, 0.19 to 0.70; \( P=0.002 \)), respectively. The strength of the association was similar in men and women. When the analyses were restricted to patients and controls without any cerebrovascular or cardiovascular history, an even stronger negative association be-

### Table 1. General Characteristics of Cases With Brain Infarction and Controls*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Cases (n=90)</th>
<th>Controls (n=180)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>72.2 (7.3)</td>
<td>72.6 (7.2)</td>
</tr>
<tr>
<td>Male sex</td>
<td>62.2 (56/90)</td>
<td>62.2 (112/180)</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>44.9 (40/89)</td>
<td>40.6 (73/180)</td>
</tr>
<tr>
<td>History of diabetes mellitus</td>
<td>25.6 (23/90)</td>
<td>14.4 (26/180)</td>
</tr>
<tr>
<td>History of hypercholesterolemia</td>
<td>23.0 (20/87)</td>
<td>26.1 (46/176)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>20.0 (18/90)</td>
<td>18.9 (34/180)</td>
</tr>
<tr>
<td>Body mass index &gt;30</td>
<td>11.5 (10/87)</td>
<td>8.7 (15/172)</td>
</tr>
<tr>
<td>At least 1 blood cholesterol assay</td>
<td>72.1 (62/86)</td>
<td>80.5 (144/179)</td>
</tr>
<tr>
<td>Antibiotic use in previous 3 mo</td>
<td>30.6 (26/85)</td>
<td>33.9 (60/177)</td>
</tr>
<tr>
<td>Chronic bronchitis</td>
<td>6.7 (6)</td>
<td>10.6 (19)</td>
</tr>
<tr>
<td>Stroke history</td>
<td>17.8 (16/90)</td>
<td>6.2 (11/179)</td>
</tr>
<tr>
<td>Cardiovascular history†</td>
<td>17.8 (16/90)</td>
<td>9.4 (17/180)</td>
</tr>
<tr>
<td>Occupation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1‡</td>
<td>57.0 (45/79)</td>
<td>53.5 (91/170)</td>
</tr>
<tr>
<td>Group 2§</td>
<td>43.0 (34/79)</td>
<td>46.5 (79/170)</td>
</tr>
</tbody>
</table>

*Conditional logistic regression for matched sets was used for comparison of proportions.
†Including myocardial infarction, coronary angioplasty, and bypass surgery.
‡White-collar workers; missing values correspond to subjects reporting no occupation.
§Employees and blue-collar workers; missing values correspond to subjects reporting no occupation.
\( P=0.04 \) for comparison between cases and controls.
\( P<0.001 \) for comparison between cases and controls.
\#P=0.05 for comparison between cases and controls.

Between brain infarction and influenza vaccination was observed (Table 2). After further adjustment for the use of antibiotics during the 3 months before the interview or history of a blood cholesterol assay (both likely to reflect general behavior regarding health consumption), the results remained significant (Table 2).

We evaluated the influence of age on the relationship between brain infarction and vaccination by performing separate analyses for subjects older and younger than 75 years. Table 3 shows that the inverse association between brain infarction and influenza vaccination was not statistically significant for patients older than 75 years and was strongly significant for patients younger than 75 years for both vaccination in the year of the study and vaccination every year during the previous 5 years.

Table 3 shows the other factors that influenced the relationship between influenza vaccination and brain infarction. We found that age was the most important factor for being vaccinated. However, risk factors or past vascular events are also important factors for being vaccinated. Among subjects who are the targets of influenza vaccination campaigns, such as diabetics and patients suffering from chronic bronchitis, we found a much lower rate of vaccination in the stroke
patients than the controls (Table 3): in stroke patients with chronic bronchitis, the vaccination rate was 17% versus 74% in the controls ($P=0.023$). However, the numbers were very small.

The associations between several variables and influenza vaccination during the preceding vaccination campaign and every year during the last 5 years were studied separately in the cases and controls. No significant associations were detected in either the cases or the controls between vaccination and the following: sex; hypertension; smoking; diabetes; hypercholesterolemia; body mass index $>$30; past cardiovascular event (including stroke); having 1, 2, or 3 risk factors; antibiotic use within the last 3 months; chronic bronchitis; having at least 1 cholesterol assay; or belonging to a higher or lower social class (data not shown). Diabetes was more frequent in subjects vaccinated during the last 5 years than in nonvaccinated subjects among both cases ($P=0.002$) and controls ($P=0.024$) (data not shown). Mean age was higher in vaccinated than nonvaccinated subjects among both cases and controls ($P=0.002$ and $P=0.012$, respectively). When the analyses were restricted to subjects with no cardiovascular or cerebrovascular history (Table 2), the association between brain infarction and vaccination (last 5 years) was not modified either overall or when the analyses were restricted to subjects with no cardiovascular or cerebrovascular history (Table 2).

### Discussion

In this study we found a negative association between influenza vaccination and brain infarction. This finding suggests that influenza vaccination protects against brain infarction. After multivariate analysis, the results remained significant despite adjustments for age, traditional risk factors, and other potential confounding variables taken as markers of the extent to which the subjects were concerned about their own general health, such as antibiotic use within the past 3 months and having had at least 1 blood cholesterol assay. After stratification by age, we found that the result was no longer significant after the age of 75 years and was strongly significant in patients younger than 75 years. One explanation could be that with increasing age, the influence of the traditional risk factors such as hypertension is too great to detect a significant direct effect of influenza vaccination. In fact, we found a very significant interaction between age and hypertension and between age and history of stroke, which are both the highest risk factors for incident stroke. Finally, since the frequencies of ischemic stroke subtypes vary according to age, it may be that influenza vaccination had a lesser effect in the subtypes more represented in the oldest patients, such as lacunar and cardioembolic strokes. Another explanation relates to the high rate of influenza vaccination in patients older than 75 years (Table 3), which perhaps makes our study underpowered to find a significant difference.

Our results are in agreement with the mounting evidence that infection may play a role in atherothrombotic disease complications. It has been shown that infections, either viral or bacterial, expose the patient to an excess of coronary or cerebral artery disease.\(^4\) --\(^5\) During large epidemics of influenza infection, an excess of mortality from heart disease has been observed.\(^6\) Subjects with chronic bronchitis are at higher risk of bacterial bronchial infections after influenza and consequently may be at higher risk of stroke. Although it is strongly recommended that these subjects should be vaccinated every year, it is striking to note the very low rate of influenza vaccination in the stroke patients in our series compared with the controls with chronic bronchitis (17% versus 74%; $P<0.02$).

Influenza vaccination has been reported to protect against recurrent myocardial infarction and primary cardiac arrest.\(^37,38\) It also reduces the rate of hospitalization for congestive heart failure.\(^39\) To our knowledge, no data concerning the influence of influenza vaccination on the incidence of stroke have been reported.

Influenza vaccination may protect against brain infarction by preventing viral infections or bacterial infections subsequent to influenza.\(^40\) Our results may add more indirect evidence that inflammation or infections may be causally related to the brain complications of atherosclerotic disease. Since influenza vaccination may also act by means of global

### Table 2: Influence of Influenza Vaccination on Brain Infarction

<table>
<thead>
<tr>
<th>Vaccinated during last vaccination season</th>
<th>OR (95% CI)†</th>
<th>OR (95% CI)‡</th>
<th>% (n)</th>
<th>OR (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>0.45 (0.24–0.84), $P=0.012$</td>
<td>0.50 (0.26–0.94), $P=0.033$</td>
<td>58.5 (62/106)</td>
<td>37.0 (0.15–0.87), $P=0.024$</td>
</tr>
<tr>
<td>Cases</td>
<td>46.7 (42/90)</td>
<td></td>
<td>42.4 (25/59)</td>
<td></td>
</tr>
<tr>
<td>Vaccinated in last 5 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>0.37 (0.19–0.70), $P=0.002$</td>
<td>0.42 (0.21–0.81), $P=0.009$</td>
<td>54.7 (58/106)</td>
<td>0.32 (0.13–0.75), $P=0.009$</td>
</tr>
<tr>
<td>Cases</td>
<td>41.1 (37/90)</td>
<td></td>
<td>35.6 (21/59)</td>
<td></td>
</tr>
</tbody>
</table>

OR indicates odds ratio.
*Adjusted for age and sex.
†Adjusted for age, sex, diabetes, hypertension, body mass index, current smoking, and cholesterol.
‡Adjusted for the same variables plus use of antibiotics in the last 3 months.
TABLE 3. Influence of Influenza Vaccination on Risk of Brain Infarction in Subgroup at Risk of Infection and in Various Subgroups That May Behave Differently With Regard to Personal Healthcare

<table>
<thead>
<tr>
<th>Vaccinated During Last Vaccination Season</th>
<th>Vaccinated in Last 5 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cases</strong> (n=90)</td>
<td><strong>Controls</strong> (n=180)</td>
</tr>
<tr>
<td><strong>Age</strong>&lt;75 y</td>
<td>33.3 (19/57)</td>
</tr>
<tr>
<td>≥75 y</td>
<td>69.7 (23/33)</td>
</tr>
<tr>
<td><strong>Sex</strong>Men</td>
<td>46.4 (26/56)</td>
</tr>
<tr>
<td>Women</td>
<td>47.1 (16/34)</td>
</tr>
<tr>
<td><strong>Diabetes</strong>Yes</td>
<td>60.9 (14/23)</td>
</tr>
<tr>
<td>No</td>
<td>32.8 (22/67)</td>
</tr>
<tr>
<td><strong>Hypertension</strong>Yes</td>
<td>55.0 (22/40)</td>
</tr>
<tr>
<td>No</td>
<td>40.8 (20/49)</td>
</tr>
<tr>
<td><strong>Smoking</strong>Yes</td>
<td>33.3 (6/18)</td>
</tr>
<tr>
<td>No</td>
<td>50.0 (36/72)</td>
</tr>
<tr>
<td><strong>Chronic bronchitis</strong>Yes</td>
<td>16.7 (1/8)</td>
</tr>
<tr>
<td>No</td>
<td>45.8 (33/72)</td>
</tr>
<tr>
<td><strong>Risk factors</strong>None</td>
<td>30.0 (6/20)</td>
</tr>
<tr>
<td>≥1</td>
<td>51.4 (36/70)</td>
</tr>
<tr>
<td><strong>Blood cholesterol assay</strong>Yes</td>
<td>48.4 (30/62)</td>
</tr>
<tr>
<td>No</td>
<td>41.7 (20/49)</td>
</tr>
<tr>
<td><strong>Use of antibiotics</strong>Yes</td>
<td>57.7 (15/26)</td>
</tr>
<tr>
<td>No</td>
<td>42.4 (25/59)</td>
</tr>
<tr>
<td><strong>Social class</strong>Low</td>
<td>50.0 (14/28)</td>
</tr>
<tr>
<td>High</td>
<td>39.4 (13/33)</td>
</tr>
</tbody>
</table>

Values are percentage (number) unless indicated otherwise.
*Adjusted for age and sex.
†Conditional logistic regression analysis adjusted for age, sex, diabetes, hypertension, body mass index, current smoking, hypercholesterolemia, past cardiovascular and cerebrovascular history, and use of antibiotics within the last 3 months.
‡Interaction between age and hypertension \((P=0.030)\) and age and past cardiovascular and cerebrovascular history \((P=0.12)\).
§Interaction between age and hypertension \((P=0.018)\) and age and past cardiovascular and cerebrovascular history \((P=0.13)\).
¶Sample size too small.
*Logistic regression analysis adjusted for age, sex, diabetes, hypertension, body mass index, current smoking, hypercholesterolemia, past cardiovascular and cerebrovascular history, and use of antibiotics within the last 3 months.
#Logistic regression analysis adjusted for age, sex, diabetes, hypertension, body mass index, current smoking, hypercholesterolemia, past cardiovascular and cerebrovascular history.
stimulation of the immune system, it would be interesting to explore whether other vaccinations have a similar protective effect on brain infarction.

Our study has several potential limitations. First, the case-control design in itself requires confirmation by other research methods, such as the conduct of prospective studies to confirm the results. Second, behavior relating to personal general health (such as cessation of smoking, a low-fat diet, and physical exercise) and awareness of the benefits of recommended preventive therapies such as influenza vaccination may be important factors influencing the occurrence of stroke. It may be argued that vaccinated subjects are the persons who are most concerned by health problems and the persons with a worse state of health and that the relationship between brain infarction and influenza vaccination is confounded by other factors that were not taken into account in our multivariate analysis. It may be that the negative association we observed between brain infarction and vaccination was not due to a direct effect of the vaccination but to the fact that being vaccinated was a marker for being at lower risk of stroke because of a better lifestyle. In fact, variables probably associated with less access to the healthcare system, such as no antibiotic use within a 3-month period, never having had a blood cholesterol assay, and having no risk factors or no previous cardiovascular disease, were associated with a considerable difference between cases and controls regarding influenza vaccination. Although we adjusted for all these variables in these subgroups, in the subgroup with chronic bronchitis and in the subgroup with a high level of occupation, the influenza vaccination variable may well have identified subjects at low risk of stroke. Consequently, patients with brain infarction appeared to be less often vaccinated. Whether the negative association we observed between brain infarction and influenza vaccination was due to a direct effect of the vaccination or to a better lifestyle can be addressed only in a prospective randomized trial. It would also be interesting to evaluate the seasonal relationship between stroke and influenza circulation.

Third, causes of brain infarction are multiple, and it is possible that the relationship between influenza vaccination and brain infarction differs according to stroke subtypes. In particular, by protecting against viral infections as well as their subsequent bacterial complications, influenza vaccination may reduce the risk of brain complications of atherosclerotic disease. We did not analyze our data according to stroke subtypes, and therefore we cannot conclude that the possible protection against brain infarction was due to a reduced rate of complications of atherosclerotic disease per se. Influenza vaccination may also favorably influence the incidence of stroke subtypes such as cardiac embolism because it reduces heart disease, which may have subsequent thromboembolic complications in the brain. Moreover, by protecting against acute bacterial and viral infections that are associated with prothrombotic states, influenza vaccination may reduce the incidence of all ischemic stroke subtypes.

In conclusion, influenza vaccination was negatively associated with ischemic stroke, particularly in patients younger than 75 years, suggesting that influenza vaccination may protect against brain infarction. Our results provide indirect evidence that infection or inflammation plays a key role in cardiovascular thrombotic events. They also open up new avenues for research into stroke prevention. Further investigation is required to establish whether a similar negative association with influenza vaccination is observed for coronary artery disease.

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References


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