

## ORIGINAL ARTICLE

# Influenza Vaccination and Reduction in Hospitalizations for Cardiac Disease and Stroke among the Elderly

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## ABSTRACT

**BACKGROUND**

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Upper respiratory tract illnesses have been associated with an increased risk of ischemic heart disease and stroke. During two influenza seasons, we assessed the influence of vaccination against influenza on the risk of hospitalization for heart disease and stroke, hospitalization for pneumonia and influenza, and death from all causes.

**METHODS**

Cohorts of community-dwelling members of three large managed-care organizations who were at least 65 years old were studied during the 1998–1999 and 1999–2000 influenza seasons. Administrative and clinical data were used to evaluate outcomes, with multivariable logistic regression to control for base-line demographic and health characteristics of the subjects.

**RESULTS**

There were 140,055 subjects in the 1998–1999 cohort and 146,328 in the 1999–2000 cohort, of which 55.5 percent and 59.7 percent, respectively, were immunized. At base line, vaccinated subjects were on average sicker, having higher rates of most coexisting conditions, outpatient care, and prior hospitalization for pneumonia than unvaccinated subjects. Unvaccinated subjects, however, were more likely to have been given a prior diagnosis of dementia or stroke. Vaccination against influenza was associated with a reduction in the risk of hospitalization for cardiac disease (reduction of 19 percent during both seasons [ $P < 0.001$ ]), cerebrovascular disease (reduction of 16 percent during the 1998–1999 season [ $P < 0.018$ ] and 23 percent during the 1999–2000 season [ $P < 0.001$ ]), and pneumonia or influenza (reduction of 32 percent during the 1998–1999 season [ $P < 0.001$ ] and 29 percent during the 1999–2000 season [ $P < 0.001$ ]) and a reduction in the risk of death from all causes (reduction of 48 percent during the 1998–1999 season [ $P < 0.001$ ] and 50 percent during the 1999–2000 season [ $P < 0.001$ ]). In analyses according to age, the presence or absence of major medical conditions at base line, and study site, the findings were consistent across all subgroups.

**CONCLUSIONS**

In the elderly, vaccination against influenza is associated with reductions in the risk of hospitalization for heart disease, cerebrovascular disease, and pneumonia or influenza as well as the risk of death from all causes during influenza seasons. These findings highlight the benefits of vaccination and support efforts to increase the rates of vaccination among the elderly.

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**S**ERIOUS COMPLICATIONS OF INFLUENZA among the elderly include pneumonia and exacerbations of coexisting conditions that can result in hospitalization or death.<sup>1</sup> Vaccination against influenza has consistently been associated with reductions in hospitalizations for pneumonia and death from all causes in the elderly.<sup>2,3</sup>

During influenza epidemics, hospitalizations for cerebrovascular and cardiovascular causes increase,<sup>4-8</sup> and acute infections, including upper respiratory tract infections, may increase the risk of acute cardiovascular<sup>9-11</sup> and cerebrovascular<sup>12-17</sup> events. Several small observational studies have suggested that influenza vaccination may be associated with a reduction in the risk of cardiac arrest,<sup>18</sup> myocardial infarction,<sup>19</sup> and acute cerebrovascular events,<sup>20</sup> although not all have found such a benefit.<sup>21</sup> In a small, unblinded, controlled trial, vaccination was also associated with lower rates of death, myocardial infarction, or revascularization among persons with an acute coronary syndrome and those scheduled to undergo percutaneous coronary intervention.<sup>22</sup> We studied two large cohorts during the 1998–1999 and 1999–2000 influenza seasons to assess whether influenza vaccination of community-dwelling elderly persons is associated with reduced rates of hospitalization for cardiac and cerebrovascular disease.

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## METHODS

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### SETTING

This is one of several studies involving the pooling of computerized data from three large managed-care organizations. Previously, we reported on the ability of vaccination against influenza to reduce the rates of hospitalization for pneumonia and influenza and death from all causes among the elderly members of these organizations<sup>23</sup> and among elderly members with specific high-risk medical conditions<sup>24</sup> during the 1996–1997 and 1997–1998 influenza seasons. The managed-care organizations are HealthPartners (650,000 members in Minnesota and Wisconsin), Oxford Health Plan (1.8 million members in New York, New Jersey, Pennsylvania, and Connecticut), and Kaiser Permanente Northwest (420,000 members in the Portland, Oregon–Vancouver, Washington area). This project was approved by the research-review boards of the health plans.

### SUBJECTS

Plan members who were at least 65 years of age on October 1, 1998 (for the 1998–1999 cohort), and October 1, 1999 (for the 1999–2000 cohort), were included in the study if they were not institutionalized and had been continuously enrolled during the preceding 12 months and throughout the outcome period. These criteria were used to ensure adequate base-line and outcome data on the subjects. In the case of the Oxford Health Plan, only members in the New York City area and adjacent counties were included, since data for the rest of the areas covered by the plan were incomplete. All elderly members of the other health plans were included.

### DATA COLLECTION AND OUTCOMES

Using uniform definitions, we obtained from the administrative and clinical data bases of each plan information on demographic characteristics (age, sex, and site); base-line coexisting conditions, defined by inpatient or outpatient diagnoses of heart disease (*International Classification of Diseases, 9th Revision, Clinical Modification* codes 093, 112.81, 130.3, 391, 393 through 398, 402, 404, 410 through 429, 745, 746, 747.1, 747.49, 759.82, 785.2, and 785.3), lung disease (codes 011, 460, 462, 465, 466, 480 through 511, 512.8, 513 through 517, 518.3, 518.8, 519.9, and 714.81), diabetes (codes 250 and 251), renal disease (codes 274.1, 408, 580 through 591, 593.71 through 593.73, and 593.9), cancer (codes 200 through 208, 140 through 198, and 199.1), vasculitis and rheumatologic disease (codes 446, 710, 714.0 through 714.4, 714.8, 714.89, and 714.9), dementia and stroke (codes 290 through 294, 331, 340, 341, 348, and 438), hypertension (code 401), atrial fibrillation (code 427.3), and lipid disorders (code 272); the number of outpatient visits during the base-line period; and the number of hospitalizations during the base-line period. The study outcomes included hospitalization for pneumonia or influenza (codes 480 through 487), acute cerebrovascular disease (codes 431 through 437), cardiac disease — ischemic heart disease (codes 410 through 414) and congestive heart failure (code 428) — and death from any cause. Influenza-vaccination status was also ascertained from the data bases, as defined by *Current Procedural Terminology* code 90657, and any site-specific flags in the clinical data bases.

### INFLUENZA SEASONS

Influenza seasons were defined by the dates that the first and last influenza isolates were obtained

**Table 1. Base-Line Characteristics of Subjects in the 1998–1999 and 1999–2000 Cohorts.\***

Characteristic	Vaccinated Subjects	Unvaccinated Subjects	P Value	Odds Ratio (95% CI)
<b>1998–1999 Cohort</b>				
No. of subjects	77,738	62,317		
Age group (%)			<0.001	—
65–74 yr	56.0	61.3		
75–84 yr	36.0	29.3		
≥85 yr	8.0	9.4		
Mean age (yr)	74.2±6.5	73.7±7.1	<0.001	—
Female sex (%)	55.4	57.4	<0.001	—
Coexisting conditions (%)				
Heart disease	26.8	23.9	<0.001	1.48 (1.44–1.52)
Lung disease	19.9	15.2	<0.001	1.50 (1.45–1.54)
Diabetes or endocrine disorders	15.2	11.4	<0.001	1.50 (1.45–1.55)
Renal disease	1.6	1.4	0.001	1.04 (0.95–1.14)
Dementia or stroke	3.8	4.8	<0.001	0.69 (0.65–0.73)
Vasculitis or rheumatologic disease	1.5	1.1	<0.001	1.33 (1.20–1.47)
Cancer	10.2	8.3	<0.001	1.18 (1.14–1.23)
Hypertension	42.2	33.1	<0.001	1.70 (1.65–1.73)
Atrial fibrillation	7.1	5.2	<0.001	1.29 (1.23–1.35)
Lipid disorder	20.7	14.5	<0.001	1.73 (1.68–1.78)
Health care use during base-line period				
No. of outpatient visits	13.0±13.1	10.6±16.1	<0.001	—
≥12 Outpatient visits (%)†	41.9	29.2	<0.001	2.04 (1.99–2.08)
Hospitalization for pneumonia or influenza (%)	1.6	1.8	0.007	0.92 (0.85–1.01)
Any hospitalization (%)	14.7	13.9	<0.001	1.06 (1.03–1.10)

in a region according to surveillance data reported to the Centers for Disease Control and Prevention. Outcomes were included if they occurred during an influenza season or within two weeks after its end in order to include delayed complications of influenza.

#### STATISTICAL ANALYSIS

Bivariable comparisons of the base-line characteristics of vaccinated and unvaccinated subjects were conducted using chi-square tests and Student's t-tests for categorical and continuous variables, respectively. Multivariable logistic regression (with SPSS 10.1 for Windows, SPSS) was used to com-

pare the study outcomes between vaccinated and unvaccinated subjects after adjustment for base-line demographic characteristics, coexisting conditions, and previous use of health care. The subject's age (65 to 74, 75 to 84, or 85 years or older) and number of outpatient visits (12 or more vs. fewer than 12 [upper one third vs. lower two thirds]) were included as categorical variables in the regression models. We estimated vaccine effectiveness by subtracting the adjusted odds ratio from 1, using the adjusted odds ratio as an approximation of relative risk. We calculated the numbers needed to treat (i.e., vaccinate) to prevent one outcome<sup>25</sup> using the following equation:  $1 \div (\text{vaccine effective-}$

<b>Table 1. (Continued.)</b>				
<b>Characteristic</b>	<b>Vaccinated Subjects</b>	<b>Unvaccinated Subjects</b>	<b>P Value</b>	<b>Odds Ratio (95% CI)</b>
<b>1999–2000 Cohort</b>				
No. of subjects	87,357	58,971		
Age group (%)			<0.001	—
65–74 yr	56.1	63.1		
75–84 yr	35.8	28.2		
≥85 yr	8.1	8.7		
Mean age (yr)	74.2±6.5	73.4±7.0	<0.001	—
Female sex (%)	55.2	56.1	0.001	—
<b>Coexisting conditions (%)</b>				
Heart disease	28.6	25.8	<0.001	1.41 (1.38–1.45)
Lung disease	20.6	16.9	<0.001	1.35 (1.32–1.39)
Diabetes or endocrine disorders	16.2	12.5	<0.001	1.46 (1.41–1.50)
Renal disease	1.7	1.5	0.007	1.03 (0.94–1.12)
Dementia or stroke	3.7	4.6	<0.001	0.73 (0.69–0.77)
Vasculitis or rheumatologic disease	1.5	1.1	<0.001	1.32 (1.20–1.46)
Cancer	10.7	8.6	<0.001	1.21 (1.16–1.26)
Hypertension	45.1	37.1	<0.001	1.61 (1.57–1.64)
Atrial fibrillation	7.2	5.4	<0.001	1.28 (1.22–1.34)
Lipid disorder	24.1	19.1	<0.001	1.56 (1.51–1.60)
<b>Health care use during base-line period</b>				
No. of outpatient visits	14.0±14.1	11.5±17.1	<0.001	—
≥12 Outpatient visits (%)†	44.6	32.0	<0.001	1.98 (1.93–2.02)
Hospitalization for pneumonia or influenza (%)	1.8	1.7	0.014	1.15 (1.06–1.25)
Any hospitalization (%)	13.6	12.7	<0.001	1.09 (1.05–1.12)

\* Plus–minus values are means ±SD. Odds ratios for coexisting conditions and health care use are for the comparison between vaccinated and unvaccinated subjects and have been adjusted for age, sex, and site. CI denotes confidence interval.

† Twelve or more outpatient visits represents the upper third for the cohort.

ness × the event rate in unvaccinated subjects). Analyses were conducted in subgroups according to age, risk (high risk, defined by one of the following coexisting conditions: heart disease, lung disease, diabetes or endocrine disorders, renal disease, stroke or dementia, vasculitis or rheumatologic disease, or cancer; and low risk, defined by the absence of any of these conditions), and site. Analyses involving a partial model (adjusted for demographic characteristics) and a complete model (adjusted for all the variables described above) were conducted to deter-

mine the effect of adjustment for covariates on the results.

To evaluate in more detail the adequacy of adjustment in the regression models, we assessed the effect of vaccination on the risk of hospitalization during the summer months after each influenza season (June through September 1999 and June through September 2000). This period was selected as a control period. We expected vaccination to provide minimal benefit then, because influenza was not circulating at those times. To account for

life-expectancy bias we estimated the ability of vaccination to reduce the rate of hospitalization during the influenza seasons after excluding everyone who died during the outcome period.

## RESULTS

There were 140,055 subjects in the 1998–1999 cohort and 146,328 in the 1999–2000 cohort. The respective rates of vaccination against influenza were 55.5 percent and 59.7 percent. At base line, vaccinated subjects were older and had a greater overall burden of illness and higher rates of health care use (Table 1). Unvaccinated subjects, however, were more likely to have been given a diagnosis of dementia or stroke. These trends persisted after adjustment for demographic characteristics (age, sex, and site) (Table 1). Both influenza seasons were characterized by the circulation of type A (H3N2) influenza viruses that were well matched to the corresponding strains included in the vaccine.<sup>26,27</sup>

During the 1998–1999 influenza season, there were 1677 and 1888 hospitalizations for study outcomes and 943 and 1361 deaths among vaccinated and unvaccinated subjects, respectively, and during the 1999–2000 influenza season, there were 1959 and 1574 hospitalizations for study outcomes and 1019 and 1026 deaths among vaccinated and unvaccinated subjects, respectively (Table 2). The rates

of all outcomes were higher among unvaccinated subjects than among vaccinated subjects.

The partial logistic-regression models included demographic characteristics (site, sex, and age, categorized as 65 to 74, 75 to 84, or 85 years or older) and vaccination status. The complete models included these variables in addition to the presence or absence at base line of various coexisting conditions (heart disease, lung disease, diabetes or endocrine disorders, cancer, renal disease, vasculitis or rheumatologic disease, dementia or stroke, hypertension, atrial fibrillation, and lipid disorders), health care use during the base-line period (12 or more outpatient visits vs. fewer than 12 outpatient visits), and the presence or absence of hospitalization for pneumonia or influenza.

Analyses involving the complete models showed that influenza vaccination in both cohorts was associated with reductions in the odds of all the study outcomes during the influenza seasons (Table 3), including hospitalization for cerebrovascular disease (reduction of 16 percent during the 1998–1999 season [ $P=0.018$ ] and 23 percent during the 1999–2000 season [ $P<0.001$ ]), cardiac disease (reduction of 19 percent during both seasons [ $P<0.001$ ]), and pneumonia or influenza (reduction of 32 percent during the 1998–1999 season [ $P<0.001$ ] and 29 percent during the 1999–2000 season [ $P<0.001$ ]) and death from all causes (reduction of 48 percent dur-

**Table 2. Outcomes during the Influenza Seasons among Vaccinated and Unvaccinated Subjects.\***

Outcome	1998–1999 Cohort		1999–2000 Cohort	
	Vaccinated Subjects (N=77,738)	Unvaccinated Subjects (N=62,317)	Vaccinated Subjects (N=87,357)	Unvaccinated Subjects (N=58,971)
	<i>number of subjects (percent)</i>			
<b>Hospitalization</b>				
Pneumonia or influenza	495 (0.6)	581 (0.9)	589 (0.7)	501 (0.8)
Cardiac disease	888 (1.1)	1026 (1.6)	1029 (1.2)	819 (1.4)
Ischemic heart disease	457 (0.6)	535 (0.9)	550 (0.6)	407 (0.7)
Congestive heart failure	466 (0.6)	538 (0.9)	525 (0.6)	454 (0.8)
Cerebrovascular disease	398 (0.5)	427 (0.7)	465 (0.5)	384 (0.7)
Any study outcome	1677 (2.2)	1888 (3.0)	1959 (2.2)	1574 (2.7)
<b>Death</b>				
Death	943 (1.2)	1361 (2.2)	1019 (1.2)	1026 (1.7)
Hospitalization or death	2387 (3.1)	2910 (4.7)	2746 (3.1)	2402 (4.1)

\* Hospitalization categories are not mutually exclusive.

ing the 1998–1999 season [P<0.001] and 50 percent during the 1999–2000 season [P<0.001]). When the odds of hospitalization for ischemic heart disease and congestive heart failure were analyzed separately, the reductions were also significant in every case except that of ischemic heart disease during the 1999–2000 season (reduction, 10 percent; P=0.12). Estimates of vaccine effectiveness were generally consistent among the age subgroups (Fig. 1A), risk subgroups (Fig. 1B), and site subgroups (Fig. 1C) for both influenza seasons. For the combined outcome of hospitalization or death, the numbers needed to treat (i.e., vaccinate) to prevent one out-

come were 61 in the 1998–1999 cohort and 68 in the 1999–2000 cohort (Table 3). Estimates of vaccine effectiveness were lower in the partial models and in some instances were 0 percent, highlighting the importance of the adjustment for coexisting conditions and health care use in the complete models (Table 3).

Vaccination against influenza was not associated with significant reductions in the odds of hospitalization during the summer months. In our subgroup analyses, which excluded subjects who died, estimates of the ability of vaccination to reduce the risk of hospitalization during the two influenza sea-

**Table 3. Effectiveness of Influenza Vaccination during the Influenza Seasons and Numbers Needed to Treat to Prevent One Outcome in the 1998–1999 and 1999–2000 Cohorts.\***

Outcome	Partial Model	Complete Model	P Value	No. Needed to Treat
	<i>odds ratio (95% CI)</i>			
<b>1998–1999 Cohort</b>				
Hospitalization				
Pneumonia or influenza	0.78 (0.69–0.89)	0.68 (0.60–0.78)	<0.001	347
Cardiac disease	1.03 (0.94–1.14)	0.81 (0.73–0.89)	<0.001	329
Ischemic heart disease	1.00 (0.88–1.14)	0.80 (0.70–0.91)	0.001	556
Congestive heart failure	1.06 (0.93–1.21)	0.81 (0.70–0.92)	0.002	585
Cerebrovascular disease	0.95 (0.82–1.10)	0.84 (0.72–0.97)	0.018	893
Any study outcome	0.93 (0.86–1.00)	0.77 (0.71–0.82)	<0.001	145
Death	0.58 (0.53–0.63)	0.52 (0.47–0.57)	<0.001	95
Hospitalization or death	0.77 (0.72–0.81)	0.65 (0.62–0.70)	<0.001	61
<b>1999–2000 Cohort</b>				
Hospitalization				
Pneumonia or influenza	0.80 (0.71–0.91)	0.71 (0.62–0.80)	<0.001	431
Cardiac disease	1.01 (0.91–1.11)	0.81 (0.73–0.89)	<0.001	376
Ischemic heart disease	1.09 (0.95–1.25)	0.90 (0.78–1.03)	0.12	—
Congestive heart failure	0.94 (0.82–1.07)	0.73 (0.64–0.84)	<0.001	463
Cerebrovascular disease	0.87 (0.75–1.00)	0.77 (0.66–0.89)	<0.001	621
Any study outcome	0.91 (0.85–0.98)	0.76 (0.71–0.82)	<0.001	154
Death	0.56 (0.51–0.62)	0.50 (0.46–0.55)	<0.001	118
Hospitalization or death	0.76 (0.72–0.80)	0.64 (0.61–0.68)	<0.001	68

\* The odds ratios for the partial models were adjusted for demographic characteristics alone (age, sex, and site). The odds ratios for the complete models were adjusted for demographic characteristics plus the presence of coexisting conditions at base line and prior health care use. The number needed to treat is the number of subjects who need to be vaccinated to prevent one outcome. The numbers needed to treat were calculated with use of the adjusted odds ratios from the complete models. P values are for the complete model. CI denotes confidence interval.

sons were virtually identical to those for the entire cohort in the two seasons (data not shown).

## DISCUSSION

In this observational study, influenza vaccination of elderly persons was associated with substantial reductions in the risk of hospitalization for cardiac disease and cerebrovascular disease during two influenza seasons. Several previous studies have suggested similar findings. In a population-based case-control study of 342 married persons who had had an out-of-hospital cardiac arrest but no other risk factors for cardiac disease, influenza vaccination during the previous 12 months was associated with a 49 percent reduction in the risk of cardiac arrest (odds ratio, 0.51; 95 percent confidence interval, 0.33 to 0.79).<sup>18</sup> In another case-control study of 109 patients in a cardiology clinic who had a myocardial infarction during the 1997–1998 influenza season, vaccination against influenza was associated with a 67 percent reduction in the risk of a myocardial infarction as compared with control subjects, who had not had a myocardial infarction (odds ratio, 0.33; 95 percent confidence interval, 0.13 to 0.82).<sup>19</sup> A case-control study of 90 patients who were 60 years of age or older and living in France and who were consecutively admitted with a stroke during the 1998–1999 and 1999–2000 influenza seasons and 180 controls found that influenza vaccination was associated with a 50 percent reduction in the risk of a stroke (odds ratio, 0.50; 95 percent confidence interval, 0.26 to 0.94).<sup>20</sup>

In addition to the observational studies, an unblinded, controlled trial of vaccination among 200 patients with acute myocardial infarction and 101 patients who were undergoing angioplasty or stent placement in Argentina found that vaccination was associated with a lower risk of death from cardiovascular causes (relative risk, 0.25; 95 percent confidence interval, 0.07 to 0.86) and of the combined end point of death, myocardial infarction, or revascularization (relative risk, 0.50; 95 percent confidence interval, 0.29 to 0.85).<sup>22</sup> Our study extends these observations from previous studies by simultaneously assessing the risk of hospitalization for cerebrovascular disease and cardiac disease as well as the more commonly evaluated influenza-associated complications of hospitalization for pneumonia and death. Furthermore, we studied large cohorts that had many outcomes, thereby increasing the power of the study. We also included data

from two influenza seasons and three geographically dispersed health care organizations, thus enhancing the generalizability of our findings to other seasons and settings.

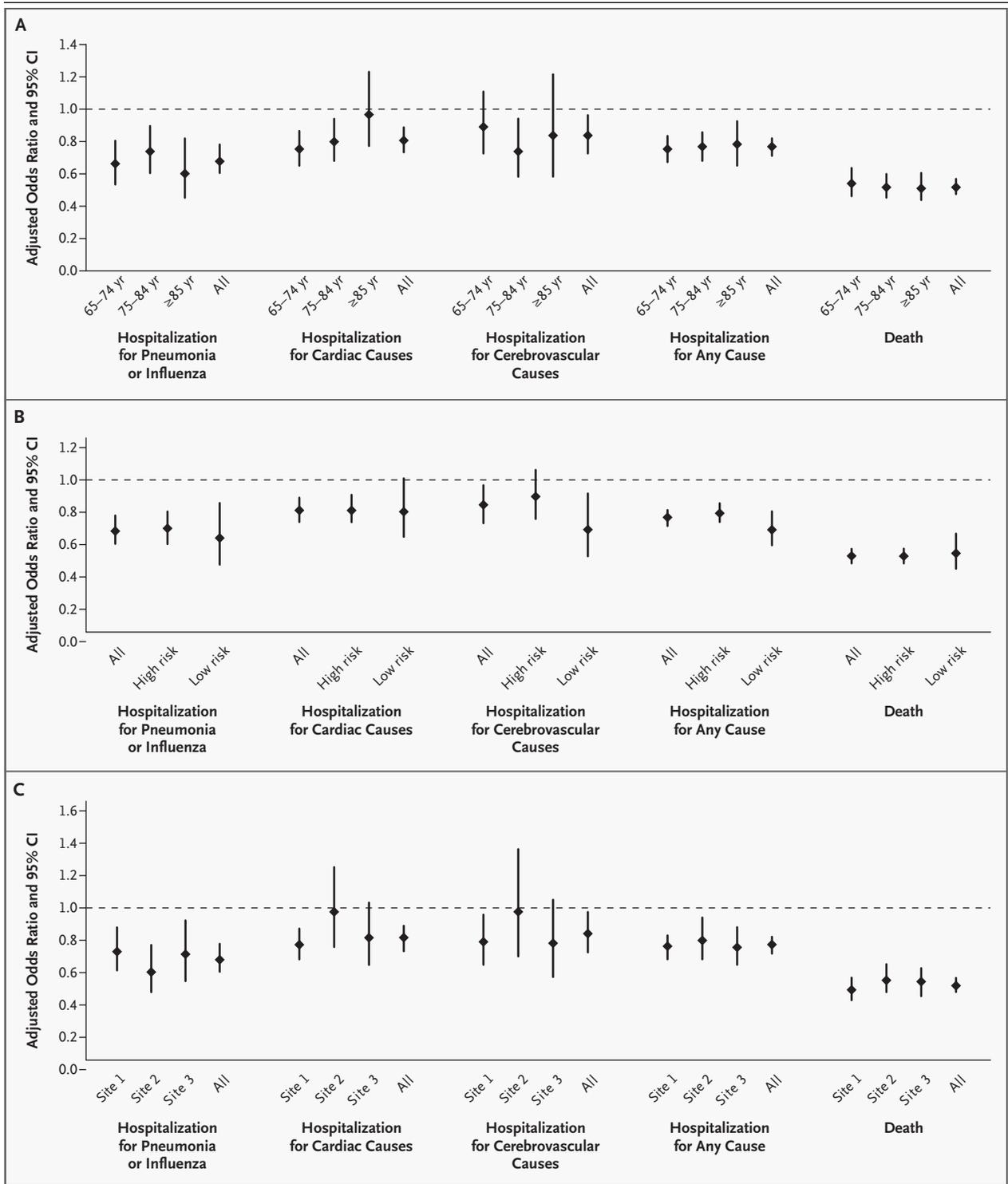
Not all reports have found that influenza vaccination protects against cardiac disease. A cohort study of 1378 patients who survived a myocardial infarction between 1992 and 1996 found no evidence that vaccination protected against recurrent coronary events after 3267 person-years of follow-up.<sup>21</sup> That study also evaluated members of health maintenance organizations, but the subjects differed from those in our study. About half were younger than 65 years of age, and all of them had survived a myocardial infarction. Certain risk factors may have a stronger influence on the risk of recurrent events among younger persons with cardiac disease than among older persons, thus making it difficult to detect benefits attributable to vaccination. Although the analytic models were similar in the two studies, the covariates included in the models were not identical, and this may also have contributed to the differences in results. In addition, the other study defined the outcome period as the six-month period from November through April. We used a more specific outcome period based on influenza-surveillance data, and this may have enhanced our ability to detect the effectiveness of vaccination. Finally, we had a larger cohort and included a broader spectrum of outcomes.

Possible mechanisms of the increased risk of cerebrovascular and cardiovascular events after upper respiratory tract illnesses such as influenza in-

**Figure 1 (facing page).** Effect of Vaccination against Influenza on the Odds Ratio for Hospitalization for Pneumonia or Influenza, Cardiac Causes, Cerebrovascular Causes, or Any Cause and the Odds Ratio for Death during the 1998–1999 Influenza Season, According to Age (Panel A), Risk (Panel B), and Study Site (Panel C).

The adjusted odds ratios and 95 percent confidence intervals (CIs) are for the comparison of vaccinated subjects with unvaccinated subjects and are from the complete regression models. High risk was defined by the presence of one of the following coexisting conditions: heart disease, lung disease, diabetes or endocrine disorders, renal disease, dementia or stroke, vasculitis or rheumatologic disease, and cancer. Low risk was defined by the absence of any of these conditions. All odds ratios have been adjusted for base-line demographic characteristics, coexisting conditions, and prior use of health care. The results of each of the subgroup analyses for the 1999–2000 season (data not shown) were similar to those for the 1998–1999 season.

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clude alterations in circulating clotting factors, platelet aggregation and lysis, concentrations of inflammatory-response proteins, and alterations in cytokine concentrations.<sup>12,28</sup> These changes might enhance thrombotic tendencies, impair vasodilation, or cause endothelial injury.

We identified vaccination-associated reductions in the risk of hospitalizations for pneumonia and influenza and death from all causes. Observational studies from various regions in the United States, Canada (Manitoba), the United Kingdom, Spain, Italy, and Argentina have also found that vaccination against influenza is associated with reductions in the risk of hospitalization for pneumonia or influenza of about 20 to 40 percent.<sup>29-38</sup> In our study, vaccination was associated with a reduction in the risk of hospitalization for pneumonia or influenza of 29 to 32 percent.

Observational studies from the United States, Manitoba, and the United Kingdom have reported that influenza vaccination is associated with reductions in the risk of death from any cause of 30 to 50 percent.<sup>23,32,33,39</sup> In our study, vaccination was associated with a reduction in the risk of death from all causes of 48 to 50 percent. This reduction may be greater than might typically be expected. Hospitalization for pneumonia and exacerbations of underlying medical conditions are well-recognized complications of influenza. Our finding that vaccination is associated with reductions in the risk of hospitalization for cardiac and cerebrovascular disease suggests additional effects of influenza that contribute to the overall disease burden and may help to explain the reduction in the risk of death associated with vaccination.

The elderly, as well as persons younger than 65 years of age who have high-risk medical conditions, are included in the high-priority groups targeted for vaccination.<sup>1</sup> Influenza vaccination is similarly effective in reducing the risk of hospitalization for pneumonia or death in healthy elderly persons and in those with coexisting conditions.<sup>24,32</sup> We found that vaccination reduced the risk of hospitalization for cardiac and cerebrovascular causes in a similar manner among both healthy and high-risk elderly persons. Many persons with high-risk medical conditions receive care from subspecialty physicians. Subspecialists, however, are less likely than generalists to recommend influenza vaccination to their high-risk patients.<sup>40</sup> Both generalists and medical subspecialists should recommend influenza vaccinations to their elderly and high-risk patients.

Our study has several potential limitations, and the results should be interpreted with caution. Because this was an observational study, we included important covariates in the analytic models. We also conducted subgroup analyses to identify possible interactions or bias in the results. Nevertheless, residual confounding may have influenced our results. Misclassification of study data, including vaccination status, is another concern. However, at one of our health plan sites, more than 90 percent of high-risk members who were vaccinated received the vaccine at a health plan site.<sup>41</sup> Furthermore, agreement between medical records and computerized data bases has been excellent, with more than 95 percent agreement at two of the study sites.<sup>23-25</sup> Even if substantial misclassification occurred, it would most likely bias the study toward negative results.

We did not collect information on pneumococcal vaccination status for the study. In contrast to influenza vaccinations, which require annual administration, pneumococcal vaccinations are usually given only once and may be effective for 6 to 10 years. We were unable to obtain the data for the prior 6 to 10 years that would be needed to characterize pneumococcal-vaccination status accurately. Pneumococcal vaccination reduces the risk of bacteremic disease but has not consistently been shown to reduce the risk of hospitalization for pneumonia.<sup>42</sup> In one study that used analytic models similar to ours, the 12-month pneumococcal-vaccination status was not a significant variable.<sup>43</sup> In another study, pneumococcal vaccination was not associated with a reduction in the risk of recurrent coronary events.<sup>21</sup> Nevertheless, if pneumococcal vaccination significantly reduces the risk of any of our study outcomes, then some of the benefits attributed to influenza vaccination may actually have been due to pneumococcal vaccination.

Influenza-associated deaths in the United States have increased significantly over the past two decades, with 90 percent occurring among the elderly.<sup>44</sup> In 2001, the rate of vaccination against influenza was only 63 percent among persons 65 years of age or older in the United States<sup>45</sup> — well below the 2010 goal of 90 percent.<sup>46</sup> Our findings highlight the benefits to be realized with vaccination and lend urgency to efforts to improve the rate of vaccination among the elderly.

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