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Effectiveness of Influenza Vaccine in the Community-Dwelling Elderly

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ABSTRACT

BACKGROUND

Reliable estimates of the effectiveness of influenza vaccine among persons 65 years of age and older are important for informed vaccination policies and programs. Short-term studies may provide misleading pictures of long-term benefits, and residual confounding may have biased past results. This study examined the effectiveness of influenza vaccine in seniors over the long term while addressing potential bias and residual confounding in the results.

METHODS

Data were pooled from 18 cohorts of community-dwelling elderly members of one U.S. health maintenance organization (HMO) for 1990–1991 through 1999–2000 and of two other HMOs for 1996–1997 through 1999–2000. Logistic regression was used to estimate the effectiveness of the vaccine for the prevention of hospitalization for pneumonia or influenza and death after adjustment for important covariates. Additional analyses explored for evidence of bias and the potential effect of residual confounding.

RESULTS

There were 713,872 person-seasons of observation. Most high-risk medical conditions that were measured were more prevalent among vaccinated than among unvaccinated persons. Vaccination was associated with a 27% reduction in the risk of hospitalization for pneumonia or influenza (adjusted odds ratio, 0.73; 95% confidence interval [CI], 0.68 to 0.77) and a 48% reduction in the risk of death (adjusted odds ratio, 0.52; 95% CI, 0.50 to 0.55). Estimates were generally stable across age and risk subgroups. In the sensitivity analyses, we modeled the effect of a hypothetical unmeasured confounder that would have caused overestimation of vaccine effectiveness in the main analysis; vaccination was still associated with statistically significant — though lower — reductions in the risks of both hospitalization and death.

CONCLUSIONS

During 10 seasons, influenza vaccination was associated with significant reductions in the risk of hospitalization for pneumonia or influenza and in the risk of death among community-dwelling elderly persons. Vaccine delivery to this high-priority group should be improved.

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Influenza continues to be a major cause of illness and death, especially among the elderly. Each year, influenza and its complications are responsible for about 186,000 excess hospitalizations for respiratory and circulatory illness[1] and 44,000 excess deaths from all causes[2] in this high-risk group. Influenza vaccines are safe and effective, and the elderly are included among the high-priority groups targeted for annual vaccination.[3]

Reliable estimates of the benefits of vaccination are important for establishing informed policies regarding resource allocation for the delivery of immunizations and identifying the need for new vaccines and strategies for the prevention and control of influenza in this group.[4] However, most studies assessing the effectiveness of influenza vaccination in the elderly have included one or only a few influenza seasons.[5] Because of the variability of influenza from season to season, the results of these short-term studies — either favorable or unfavorable — might provide incomplete or misleading pictures about the benefits of vaccination over longer periods of time[6]; furthermore, heterogeneity between studies may limit the ability to pool results appropriately across studies.[7]

Because of ethical constraints imposed by recommendations that target the elderly for annual vaccination, most studies of the effectiveness of influenza vaccine in elderly persons have been observational studies and not randomized, controlled trials. Questions have been raised about the effects of potential bias and residual confounding on past estimates of vaccine effectiveness from these observational studies.[8,9]

In this study, we analyzed the effectiveness of influenza vaccination among 18 cohorts of community-dwelling elderly members of health maintenance organizations (HMOs) during 10 seasons. Our purpose was to provide a long-term view of the effectiveness of influenza vaccine while addressing potential bias and residual confounding.

Methods

We pooled subject-level data from 18 cohorts of elderly members of one U.S. HMO for the 1990–1991 through the 1999–2000 seasons and of two other U.S. HMOs for the 1996–1997 through the 1999–2000 seasons. Each cohort provided data for more than 20,000 person-seasons, for a total of 713,872 person-seasons during 10 seasons. The study authors were solely and independently responsible for the study design, the data analysis, the writing and preparation of all drafts of the manuscript, and the submission of the manuscript. The basic study design and methods have been described previously.[10-13] The institutional research committees of the HMOs approved the project. Informed consent was not required.

Study Sites and Participants

The participating HMOs were HealthPartners in Minnesota and Wisconsin (1990–1991 through 1999–2000); Kaiser Permanente Northwest in the Portland, Oregon, and Vancouver, Washington, area (1996–1997 through 1999–2000); and Oxford Health Plans in New York City and surrounding counties (1996–1997 through 1999–2000). All noninstitutionalized members of the plans were included in that season's cohort if they were 65 years of age or older as of October 1, had been continuously enrolled in the plan for the preceding 12 months, were alive on the first day of the influenza season, and were either continuously enrolled or died during the outcome period. We selected these criteria to ensure adequate baseline and follow-up data and to reduce the potential for survivor bias.

Study Data

Data were extracted retrospectively from the administrative and clinical databases of the HMOs by the HMO research teams using standardized definitions that were consistent across the 10 seasons. Data elements included age, sex, baseline coexisting medical conditions (defined according to outpatient or inpatient *International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] codes denoting heart disease, lung disease, diabetes, renal disease, hematologic or nonhematologic cancer, vasculitis or rheumatologic disease, dementia or stroke, and immune deficiency or organ transplantation), health care use during the previous 12 months (the number of hospitalizations and outpatient visits), year, site, and influenza-vaccination status. The study outcomes included hospitalization for pneumonia or influenza (ICD-9-CM codes 480 through 487) and death from any cause.

Influenza Seasons

Region-specific dates for the first and last influenza isolates reported to the Centers for Disease

Control and Prevention defined the influenza seasons. Outcomes were included if they occurred during this period or, to capture delayed complications, within 2 weeks after the end of the influenza season.

STATISTICAL ANALYSIS

The baseline characteristics of vaccinated and unvaccinated subjects were compared with the use of the chi-square test and Student's t-test. Logistic regression (SPSS for Windows, version 13.0) was used to compare study outcomes between vaccinated and unvaccinated subjects after adjustment for covariates. The propensity score (the probability of being vaccinated given the observed covariates) was calculated for each subject and was included in the models with the use of strata based on quintiles of propensity score.[14] Demographic characteristics, coexisting medical conditions, previous use of health care, site, and year were also included. Age (65 to 69 years, 70 to 79 years, 80 to 89 years, and 90 years and older) and number of outpatient visits (<4, 4 to 8, 9 to 15, and >15) were included as categorical variables. A similar model derived from and validated among vaccinated and unvaccinated cohorts from the three HMOs for the 1996–1997 and 1997–1998 seasons discriminated well between persons who did or did not enter the hospital or die during the influenza season.[15] Vaccine effectiveness was estimated as a percentage: (1 − adjusted odds ratio) × 100.

We conducted subgroup analyses to explore for heterogeneity in levels of vaccine effectiveness and to divide the study population into more homogeneous strata that might reduce the effect of residual confounding or bias.[16] The subgroups were defined by sex, age, risk status (high risk was defined as the presence of one or more major coexisting conditions at baseline, and low risk as the presence of no major coexisting conditions at baseline), propensity-score quintile, previous hospitalization, and previous use of outpatient care. To test for a healthy-vaccinee bias, we compared the risk of hospitalization for vaccinated and for unvaccinated persons during noninfluenza periods; data about hospitalization but not about mortality were available for the summer months of June through September after the 1998–1999 and 1999–2000 influenza seasons.

For our sensitivity analysis, we modeled how a hypothetical unmeasured confounder might have influenced our estimates of vaccine effectiveness.

Table 1. Baseline Characteristics of the Study Subjects.*

Characteristic	Unvaccinated (N = 298,623)	Vaccinated (N = 415,249)
Age (yr)	73.6±6.9	73.9±6.3
Male sex (%)	41.7	44.4
Presence of one or more high-risk medical conditions (%)	45.6	55.6
Diabetes	11.0	14.4
Heart disease	22.7	26.8
Lung disease	15.2	19.2
Renal disease	2.0	2.3
Vasculitis or rheumatologic disease	1.4	1.9
Immune deficiency	1.0	1.2
Cancer	13.3	14.5
Dementia or stroke	4.7	3.4
No. of outpatient visits during baseline period	10.3±15.6	12.8±13.3
Hospitalization during baseline period (%)	13.3	14.5

* Plus–minus values are means ±SD. All P values are less than 0.001.

In our main analyses, vaccinated subjects appeared sicker than unvaccinated subjects, and we controlled for those measured differences. If an unmeasured confounder were also present so that persons with the confounder were less likely to be vaccinated but more likely to be hospitalized or die, then our main analyses would have overestimated vaccine effectiveness.[17] Some examples of possible unmeasured confounders are race, income, and functional status. Limited data for two of the HMOs, however, suggest that the study populations were racially fairly homogeneous, with 85 to 90% of persons indicating that they were white (unpublished observations). Other investigators have reported that, after age, sex, and coexisting conditions have been controlled for, functional status is a stronger predictor of hospitalization or death among the elderly than is income.[18] We therefore modeled our hypothetical confounder on the basis of published data about impaired functional status in the elderly.

On the basis of previous studies of functional status and the observed levels of association between important covariates with outcomes in our multivariable models, we estimated that plausible associations with vaccination and outcomes for a strong confounder would mean that persons with the confounder would be half as likely to be vac-

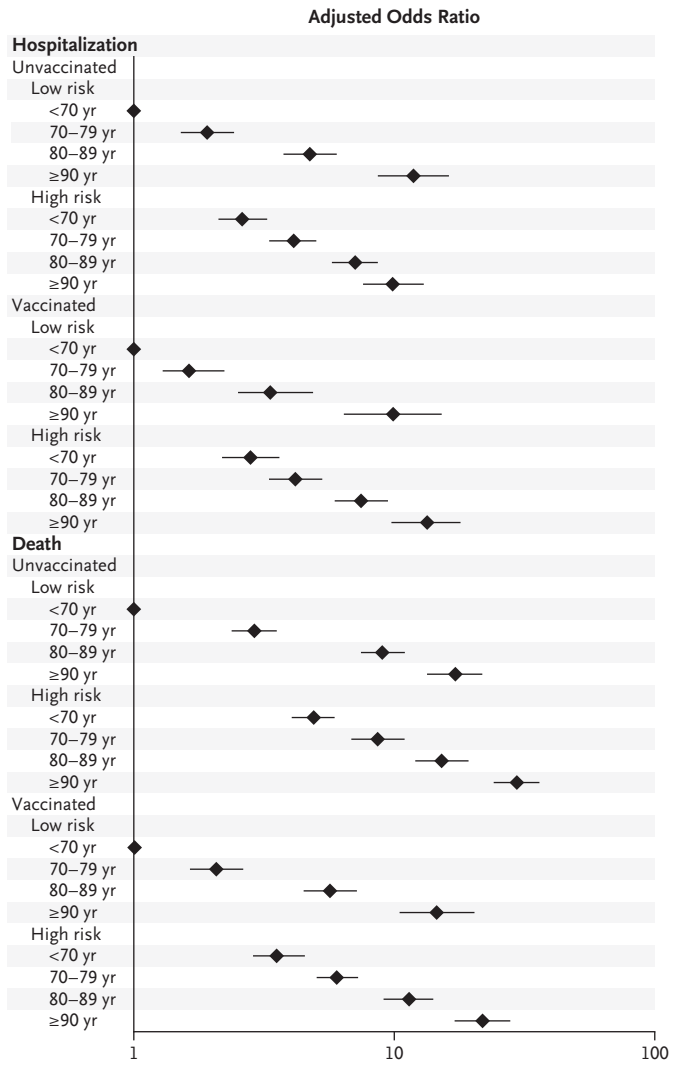

Figure 1. Risk of Outcomes According to Age and Risk Status for Unvaccinated and Vaccinated Groups.

Shown are the adjusted odds ratios, with bars indicating the 95% confidence intervals. The reference category (with an odds ratio of 1) for both outcomes within each group was persons at low risk who were under 70 years of age. High risk is defined as having one or more major coexisting conditions at baseline, and low risk as having no major coexisting conditions at baseline.

cinated[19] and two to three times as likely to be hospitalized or die[18,20-22] as would persons without the confounder. We varied the prevalence of the confounder from 20 to 60%.[23] The method of Lin et al.[24] was used to quantify the effect of the hypothetical confounder on our estimates of vaccine effectiveness. All reported P values are two-sided and were not adjusted for multiple testing.

RESULTS

There were 713,872 person-seasons of observation. Vaccinated subjects were slightly older and had higher prevalence rates of all the baseline medical conditions except dementia or stroke (Table 1).

The predominant circulating virus strains for the 10 influenza seasons were type A/H3N2 for 6 seasons (1991–1992, 1993–1994, 1996–1997, 1997–1998, 1998–1999, and 1999-2000), type B for 1 season (1990–1991), mixed A/H3N2 and B for 2 seasons (1992–1993 and 1994–1995), and mixed A/H3N2 and A/H1N1 for 1 season (1995–1996).[1,2] The vaccine–virus antigenic match was good to excellent in all seasons except 1992–1993 and 1997–1998, when the circulating A/H3N2 strains represented drifted variants.[10,12]

During the 10 influenza seasons, there were 4599 hospitalizations for pneumonia or influenza and 8796 deaths. The observed hospitalization rates for unvaccinated and for vaccinated participants were, on average, 0.7% and 0.6% per season, respectively, with corresponding death rates of 1.6% and 1.0% per season. Increasing age and the presence of one or more high-risk medical conditions at baseline were the strongest predictors of the risk of hospitalization or death in our models, with patterns of increasing risk being virtually identical for vaccinated and for unvaccinated persons (Fig. 1).

Influenza vaccination was associated on average with substantial reductions in hospitalizations for pneumonia and for influenza (vaccine effectiveness, 27%; adjusted odds ratio, 0.73; 95% confidence interval [CI], 0.68 to 0.77) and in death (vaccine effectiveness, 48%; adjusted odds ratio, 0.52; 95% CI, 0.50 to 0.55). Estimates varied from season to season and across the 18 cohorts (Fig. 2). In the two seasons with a poor match between the vaccine and the virus strain, vaccine effectiveness was lower for reducing death (in seasons with a poor match, vaccine effectiveness was 37% [adjusted odds ratio, 0.63; 95% CI, 0.57 to 0.69]; in seasons with a good match, vaccine effectiveness was 52% [adjusted odds ratio, 0.48; 95% CI, 0.46 to 0.51]) but not for reducing hospitalization. Our multivariable regression models showed good to excellent discrimination, with C statistics of 0.76 (95% CI, 0.75 to 0.77) for hospitalization and 0.81 (95% CI, 0.80 to 0.81) for death.

Estimates of vaccine effectiveness suggested clinically significant benefits across the subgroups

(Fig. 3). There was, however, evidence for interaction between vaccination and high-risk status for hospitalization (P=0.004) and between vaccination and sex (P=0.03) and outpatient visits (P=0.03) for death. All other P values for interaction between vaccination and subgroup variables were greater than 0.05. Our analysis for evidence of a healthy-vaccinee bias was negative; during the two noninfluenza periods for which we had information, vaccinated and unvaccinated persons had similar risks of hospitalization (for June through September 1999, the adjusted odds ratio was 1.0 [95% CI, 0.78 to 1.28]; for June through September 2000, the adjusted odds ratio was 0.94 [95% CI, 0.74 to 1.19]).

The sensitivity analysis shows how our estimates of vaccine effectiveness might have been influenced by residual confounding (Table 2). With increasing prevalence of the confounder and with increasing risk of an outcome because of the confounder, estimates of vaccine effectiveness were incrementally lower though still significant. In the most extreme scenario that we evaluated, at a prevalence of 60% and an increased risk by a factor of three of an outcome, the estimates of vaccine effectiveness were reduced to 7% for hospitalization and 33% for death.

DISCUSSION

In this study, influenza vaccination of community-dwelling elderly persons during 10 seasons was associated with substantial reductions in hospitalizations for pneumonia or influenza and in death. By pooling patient-level data from 18 cohorts spanning the decade of the 1990s and including 713,872 person-seasons of observation, we have provided an important perspective on the benefits of vaccination among the elderly. We documented both the year-to-year variability that can be seen and the average long-term level of benefit from vaccination. Previous case–control and cohort studies from other populations and countries have also demonstrated benefits of vaccination in elderly populations.[5,6] However, the limitations of studies based on a single or just a few influenza seasons, because of the substantial variability from year to year in circulating viruses and in antigenic match between circulating viruses and vaccine strains, and the challenges associated with attempts to pool results from heterogeneous studies in the absence of patient-level data[6,7] have been acknowledged. Our study during 10 consecutive seasons attempts to overcome these limitations.

The large number of subjects in our data set permitted considerable precision in our estimates, which showed substantial benefits across multiple subgroups, a result suggesting that vaccination benefits probably extend to a broad spectrum of elderly persons. We also included subjects from

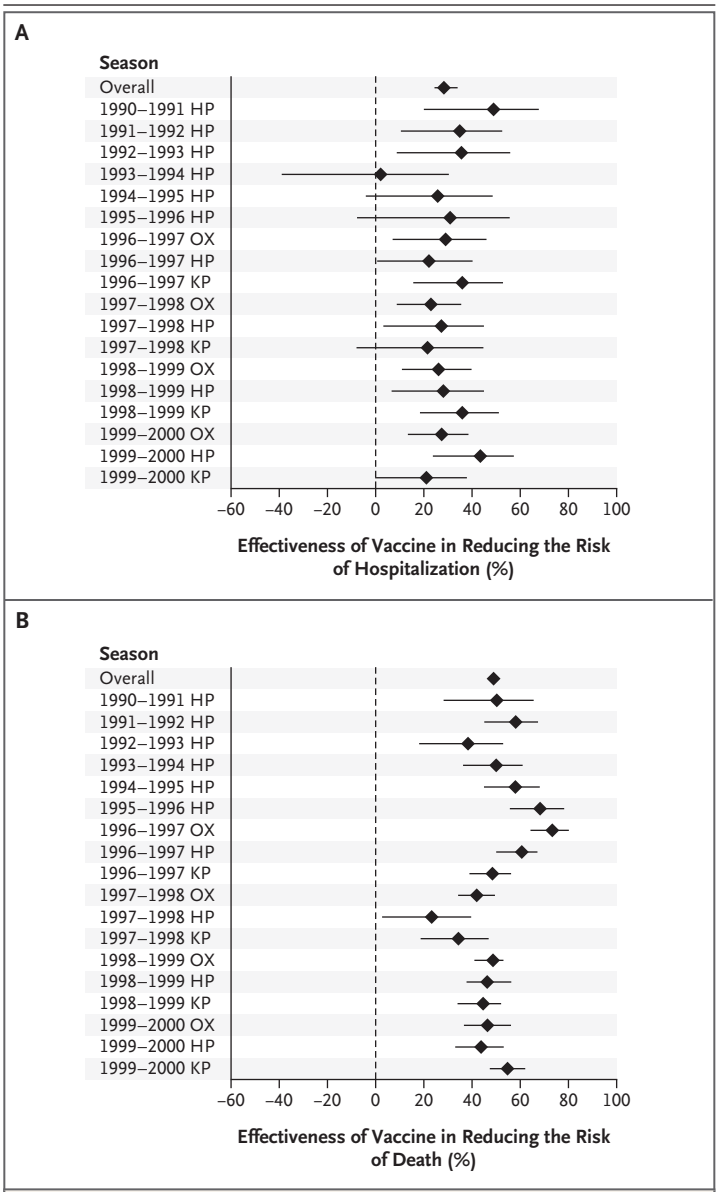

Figure 2. Effectiveness of the Influenza Vaccine in Reducing the Risk of Hospitalization for Pneumonia or Influenza (Panel A) and Death (Panel B).
The estimates of vaccine effectiveness were calculated as (1 − adjusted odds ratio) × 100. The bars indicate the 95% confidence intervals. HP denotes HealthPartners, OX Oxford Health Plans, and KP Kaiser Permanente.

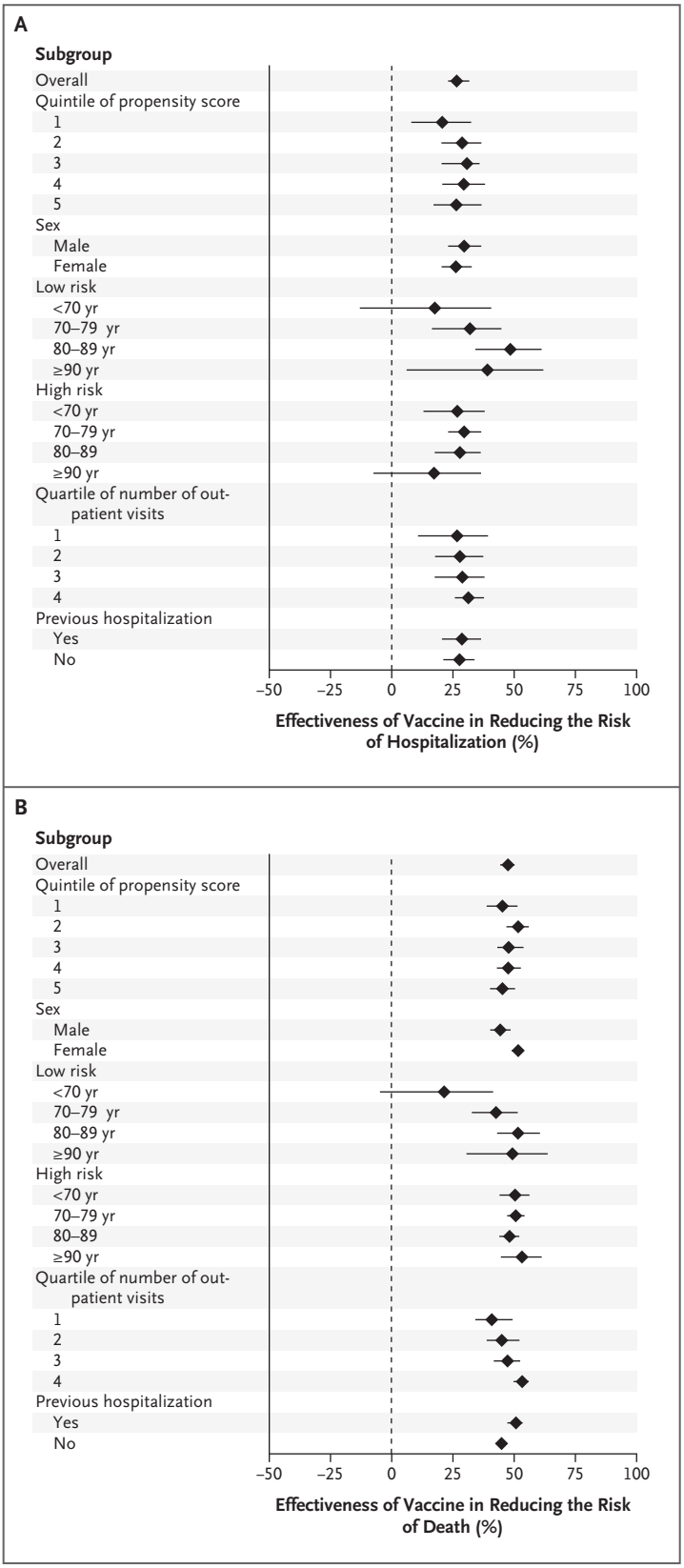

Figure 3. Results of the Subgroup Analyses Assessing Vaccine Effectiveness in Reducing the Risk of Hospitalization (Panel A) and Death (Panel B).

The subgroups included quintile of propensity score, sex, age, risk group (high risk was defined as the presence of one or more major coexisting conditions at baseline, and low risk as the presence of no major coexisting conditions at baseline), quartile of the number of outpatient visits during the baseline period, and previous hospitalization during the baseline period. Estimates of vaccine effectiveness were calculated as (1 − adjusted odds ratio) × 100, with bars indicating the 95% confidence intervals. There was interaction between vaccination and high-risk status for hospitalization ($P=0.004$), between vaccination and sex for death ($P=0.03$), and between vaccination and outpatient visits at baseline for death ($P=0.03$). All other P values for interaction between vaccination status and subgroups were greater than 0.05.

three geographically diverse HMOs to enhance the likelihood that our study population would be representative of other HMO populations across the country. However, elderly enrollees in HMOs may differ from elderly persons without HMO coverage in important ways, including race, income, functional status, and urban versus nonurban residence,[25] and caution should be used in generalizing our results to other groups.

In addition, our study was not designed to evaluate levels of vaccine effectiveness among the frailest elderly, such as those living in nursing homes. The elderly may have impaired humoral[26] and cell-mediated[27,28] immune responses to influenza vaccines. Institutionalized and other frail, elderly persons may be especially likely to exhibit such impaired immune responses,[29,30] and therefore the levels of vaccine effectiveness in this population may be lower than those we have reported for the community-dwelling elderly.

Inactivated influenza vaccines are most effective when there is a good match between circulating viruses and vaccine strains; protection may also be substantial, though sometimes lower, during years with a poor match among healthy young adults,[31,32] healthy adults and adults at high risk aged 50 through 64 years,[33] and institutionalized elderly persons.[34] Our findings are similar. During the two seasons with a poor match in our study, vaccination was associated with significant reductions in hospitalization and death, although the reduction in the risk of death was smaller than it was during the seasons with a good match.

Our results provide useful information on the

Table 2. Sensitivity Analysis to Quantify the Effects of a Hypothetical Unmeasured Confounder on the Study Results.*

Increase in the Risk of Outcome on Account of the Confounder	Prevalence of Confounder	Hospitalization for Pneumonia or Influenza		Death	
		Vaccine Effectiveness	Adjusted Odds Ratio (95% CI)	Vaccine Effectiveness	Adjusted Odds Ratio (95% CI)
	%	%		%	
—	0	27	0.73 (0.68–0.77)	48	0.52 (0.50–0.55)
Doubled	20	20	0.80 (0.75–0.85)	43	0.57 (0.55–0.60)
Doubled	40	15	0.85 (0.80–0.90)	40	0.60 (0.58–0.63)
Doubled	60	14	0.86 (0.81–0.92)	39	0.61 (0.59–0.65)
Tripled	20	14	0.86 (0.81–0.92)	38	0.62 (0.59–0.64)
Tripled	40	9	0.91(0.86–0.97)	35	0.65 (0.63–0.69)
Tripled	60	7	0.93 (0.87–0.99)	33	0.67 (0.64–0.70)

* We modeled our hypothetical confounder on impaired functional status in the elderly. The results of the main analysis without adjustment for the hypothetical unmeasured confounder are shown in the first row, which shows a prevalence of 0. Persons with the confounder were assumed to be half as likely to be vaccinated as persons without it. Vaccine effectiveness is estimated as (1 − adjusted odds ratio) × 100. Adjusted odds ratios in the presence of the hypothetical confounder were estimated by the method described by Lin et al.[24]

benefits that elderly persons may receive from vaccination. How these results might relate to population-level trends is unclear. For example, influenza-attributable excess mortality rates in the United States have not declined to the degree that might be expected in light of increasing vaccination rates during the 1980s and the early 1990s.[35] However, nation-level data do not include the risk profile or vaccination status of those who have died. Critical information is therefore lacking, making it difficult to estimate what the expected excess mortality rates would be if vaccination rates were 0%, what benefits have already been realized given current patterns of vaccine use, and what additional benefits might be realized with more effective vaccine delivery. Because of the large geographic variations in vaccine delivery in the United States, as well as disparities in vaccination rates according to race and ethnic group,[36] the aging of the population,[2] and the increasing numbers of elderly persons with high-risk conditions[37,38] for whom the risk of dying increases exponentially, attempts to correlate population-level trends with individual levels of protection due to vaccination or vice versa will be susceptible to many pitfalls, including the ecologic fallacy.[39]

This study has several limitations. Because this was an observational study, we adjusted for important covariates in our analytic models. These models discriminated well between persons who did and those who did not become hospitalized or die. Our inclusion criteria were designed to minimize the possibility of survivor bias, and we did not find evidence for a healthy-vaccinee effect in our analyses. Nevertheless, residual confounding may have influenced our results, and our sensitivity analyses indicate how our estimates of vaccine effectiveness would be lower, though still significant, after adjustment for the effect of a strong hypothetical unmeasured confounder. Misclassification of vaccination status may also have occurred; the most likely cause of misclassification would have been a failure to record receipt of vaccine. However, at one of the HMOs, more than 90% of members at high risk who were vaccinated received the vaccine at a health plan site.[40] Furthermore, agreement between medical records and computerized databases has been excellent, with more than 95% agreement at two of the study sites.[12] Even if substantial misclassification occurred, it probably would have biased the results toward the null hypothesis.

Achieving optimal success in preventing and controlling influenza among the elderly may require more immunogenic vaccines and new strategies that induce greater levels of herd immunity and thereby interrupt influenza transmission in communities. More effective vaccines for the el-

derly are under development but have not yet been approved for use in the United States. Vaccination of children in the United States has been associated with reductions in illness in households[41] and in the community,[42] and in Japan with lower mortality rates among the elderly.[43] However, these studies are not conclusive,[44,45] and additional research is needed to define the benefits among the elderly that might be realized from vaccinating children. In the meantime, vaccination rates of elderly persons remain stagnant and well below the 2010 goal of 90%.[3] Even as we wait for new vaccines and new strategies, patients, their health care providers, and policymakers should renew efforts to improve the delivery of current influenza vaccines to this high-priority group. Hospitalizations and deaths will be prevented if we can succeed.

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