Influenza Vaccination and Risk of Mortality Among Adults Hospitalized With Community-Acquired Pneumonia

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Background: Influenza vaccination has been shown to reduce illness and all-cause mortality in vulnerable populations through the prevention of influenza infection. Attenuation of the severity of illness by vaccination has been reported for respiratory tract infections due to bacterial pathogens and would represent an important additional health benefit of influenza vaccination. We evaluated the impact of prior influenza vaccination on in-hospital mortality and other health outcomes among hospitalized adults with community-acquired pneumonia (CAP).

Methods: Consecutive individuals hospitalized with CAP during “influenza season” (November to April, 1999-2003) at hospitals operated by Tenet HealthCare were identified using a database constructed to improve quality of patient care. Associations between vaccination status and all-cause in-hospital mortality were evaluated using logistic regression models.

Results: Among 17 393 adults hospitalized with CAP during the study period, 1590 (19% of those with recorded vaccine status) had a history of influenza vaccination in the current or most recent influenza season. Vaccine recipients were less likely to die in hospital of any cause than individuals without vaccination (odds ratio, 0.30; 95% confidence interval, 0.22-0.41). These effects remained significant after adjustment for the presence of comorbid illnesses and pneumococcal vaccination (adjusted odds ratio for death, 0.61; 95% confidence interval, 0.43-0.87) and under widely varying assumptions about individuals with missing vaccination status.

Conclusions: Prior influenza vaccination was associated with improved survival in hospitalized patients with CAP during influenza season. This observation, if confirmed by other studies, would represent an important additional benefit of enhanced influenza vaccine coverage.

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Influenza A and B viruses are important causes of morbidity and mortality in the United States and elsewhere. Seasonal circulation of influenza viruses is associated with a predictable surge in diagnosed influenza and pneumonia, as well as hospital admissions for acute exacerbations of chronic illness (eg, congestive heart failure and chronic renal insufficiency), with resultant increases in population mortality. The annual economic costs of influenza-related hospitalizations have been estimated at between $400 million and $1 billion in the United States alone, and additional costs accrue from lost productivity due to influenza in otherwise healthy workers. Recently, concern has heightened with respect to the potential for influenza viruses to cause severe illness in children and the likelihood of a destructive influenza pandemic, possibly larger in extent than that seen in 1919, perhaps as a result of human-to-human transmission of highly pathogenic avian influenza viruses.

Vaccination is the current mainstay of prevention efforts aimed at influenza viruses. It has been noted that influenza vaccine reduces all-cause mortality and hospitalization in older adults and reduces absences from work in otherwise healthy young adults. Notwithstanding these benefits, influenza vaccination remains underused by those at greatest risk of complications of influenza. Suboptimal levels of vaccine use may be due, at least in part, to the recognition of incomplete protection against influenza by vaccination in high-risk individuals. Older individuals appear to be at particular risk for vaccine failure, perhaps as a result of immune senescence. Nonetheless, vaccination may confer benefits.
even if infection is not prevented; for example, vaccinated individuals may have attenuated illness, which could decrease their risk of experiencing downstream complications of influenza infection. Attenuation of disease severity has been described for some vaccines (notably the 23-valent polysaccharide vaccine against \textit{Streptococcus pneumoniae}),\textsuperscript{17,18} and limited data suggestive of a similar effect are available for nonreplicating influenza vaccines.\textsuperscript{19,20} Reduction in illness severity, even among those who are not protected against infection, would enhance the population health benefits of this vaccine.

We sought to identify and quantify protective effects conferred by current influenza vaccination in a large cohort of individuals hospitalized with lower respiratory tract infection in community and teaching hospitals widely distributed across the United States. In this population, by definition, influenza vaccination has been ineffective in preventing pneumonia and hospitalization, such that vaccination-attributable health gains are likely to be due to attenuation, rather than prevention, of disease. This approach also provides an opportunity to study vaccination effects in a population that is by definition at risk of pneumonia; as such, observed effects of vaccination are not due to differences in pneumonia risk between vaccinated and unvaccinated individuals.

### METHODS

#### STUDY POPULATION

Study subjects were adults (age ≥18 years) admitted to acute care hospitals operated by Tenet Healthcare Corporation, Dallas, Tex, with a diagnosis of community-acquired pneumonia (CAP) (\textit{International Classification of Diseases, Ninth Revision, Clinical Modification} [ICD-9-CM] codes 480.0-487.0) during 4 influenza seasons (November to April) occurring between November 1999 and April 2003. When more than 1 record was available for a single individual, only the first was included in the analysis.

Systematic data collection was performed as part of a system-wide quality improvement initiative known as the “Partnership for Change” (PFC), initiated in 38 Tenet-operated hospitals in 1999. The program was designed to evaluate clinical outcomes and hospital performance in sentinel medical conditions, one of which was CAP, and was subsequently extended to all Tenet institutions. Data collected by trained nurse case managers who concurrently gave patient care were entered directly into the database using laptop computers. Primary diagnoses were validated through reconciliation with discharge ICD-9-CM codes at the end of each month to ensure completeness and accuracy of coding by case managers. Standard data collection instruments and definitions were used in all hospitals, and guidelines for clinical abstraction were available on the health system’s internal Web site. A full-time corporate education director was responsible for ensuring consistency in data collection methods at all sites.

Although 109 hospitals ultimately participated in the PFC, we restricted our analyses to patients admitted to 34 institutions (33 community hospitals and 1 teaching hospital), which had contributed data in the 4 consecutive influenza seasons starting in November 1999. These hospitals were located in California (n = 17), Florida (n = 9), Louisiana (n = 5), and Missouri (n = 3). A complete list of institutions represented in this data set is presented in at the end of this article.

### SEVERITY OF PNEUMONIA, VACCINATION STATUS, AND CLINICAL OUTCOMES

Data on age, sex, medical history, nursing home residence, vital signs, clinical and radiographic findings, and laboratory values on hospital admission, sufficient for the calculation of Pneumonia Outcomes Research Team (PORT) scores,\textsuperscript{21} were collected routinely for all patients with CAP. The PORT score is a validated clinical prediction rule that permits risk stratification regarding the likelihood of adverse outcomes in individuals with CAP. Calculation of the PORT score is based on such factors as patient age, sex, nursing home residence, physical examination and laboratory findings, and preexisting comorbid illnesses. Individuals with a score of 4 or greater on a 1 to 5 scale appear to be at markedly increased risk of in-hospital death.\textsuperscript{21}

Records of comorbid conditions not used for calculation of PORT scores, but which themselves constitute an indication for pneumococcal vaccination (ie, infection with human immunodeficiency virus, diabetes mellitus, and chronic obstructive pulmonary disease), were also available.\textsuperscript{22} Microbiological data were not available.

Data on current vaccination against influenza, as well as lifetime vaccination against \textit{S pneumoniae}, were routinely collected by case managers as part of an effort to ensure that unvaccinated individuals receive appropriate immunizations prior to discharge from hospital.\textsuperscript{21} Individuals admitted during influenza season were considered to have current vaccination if vaccinated since the beginning of the current influenza season (ie, subsequent to the October preceding the beginning of influenza season). Data on vaccination status was derived from a variety of sources (including direct communication with the patient’s primary care physician, interview with the patient or the patient’s proxy, liaison with the patient’s long-term care institution if appropriate, or review of the patient’s medication record).

Vaccine status was recorded as “received,” “not received,” or “unknown.” Data on vaccination against influenza during prior influenza seasons were not available, though data on the nonreceipt of influenza vaccination because of a prior adverse reaction to influenza vaccine was available. Subject discharge status was coded as “alive” or “dead” by case managers. Disposition of individuals alive at discharge was classified as discharge home; discharge to a long-term care institution, skilled nursing facility, or rehabilitation facility; or transfer to another acute care hospital. Complications that occurred during hospitalization, including respiratory failure, “septic shock,” in-hospital myocardial infarction, acute renal failure, and upper gastrointestinal bleeding, were recorded by case managers.

### STATISTICAL ANALYSIS

The baseline demographic characteristics and health status of individuals with and without current influenza vaccination and with unknown vaccine status were compared using χ² tests for categorical variables, and 1-way analysis of variance (ANOVA) for continuous variables.\textsuperscript{24} Crude rates of all-cause in-hospital mortality, based on reported vaccine status, were generated using Kaplan-Meier methods, with pairwise comparison of survival performed using the log-rank test.\textsuperscript{25}

Crude and adjusted odds ratios for all-cause in-hospital death and other adverse outcomes with a documented history of current influenza vaccination were generated through construction of univariable and multivariable logistic regression models.\textsuperscript{26} Multivariable models were adjusted for subjects’ PORT scores; additional covariates that were associated with likelihood of vaccination in univariable analyses were added to mul-
The database included records of 38,001 consecutive admissions for CAP occurring during the 4 influenza seasons falling between November 1999 and April 2003. Of these records, 382 represented repeated admissions of a single individual, 2918 were for subjects younger than 18 years, and 17,308 were from hospitals that joined the PFC subsequent to the 1999-2000 influenza season, such that a total of 17,393 subject records were available for analysis.

Influenza vaccination status (vaccinated or unvaccinated) was available for 8251 subjects (47%). Among those with recorded vaccination status, 1590 (19%) had record of current influenza vaccination. Significant differences were seen between individuals with current vaccination, without current vaccination, and with unknown vaccine status with respect to all evaluated covariates except sex. Of note, vaccinated individuals were older, had higher acuity of illness (as reflected in higher PORT scores), and were less likely to be smokers and nursing home residents compared with individuals without current influenza vaccination or with unknown vaccine status. The prevalence of selected comorbidities, including prior diagnosis of cancer, leukemia, and chronic obstructive pulmonary disease, was significantly higher among nonvaccinated individuals than among those with current influenza vaccination (Table 1).

All-cause mortality during hospitalization occurred in 1245 individuals (7%). Individuals with documented current influenza vaccine were less likely to die during hospitalization compared with documented nonrecipients (crude odds ratio [OR], 0.30; 95% confidence interval [CI], 0.22-0.41) and less likely to be smokers and nursing home residents compared with individuals without current influenza vaccination or with unknown vaccine status. The prevalence of selected comorbidities, including prior diagnosis of cancer, leukemia, and chronic obstructive pulmonary disease, was significantly higher among nonvaccinated individuals than among those with current influenza vaccination (Table 1).

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### Table 1. Characteristics of Study Population According to Recorded Current Influenza Vaccination Status*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Vaccinated (n = 1590)</th>
<th>Unvaccinated (n = 6661)</th>
<th>Unknown Status (n = 9142)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD, y</td>
<td>71.5 ± 17.3</td>
<td>71.5 ± 17.9</td>
<td>72.3 ± 17.3</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Female sex</td>
<td>695 (43.7)</td>
<td>3012 (45.2)</td>
<td>4144 (45.3)</td>
<td>.48</td>
</tr>
<tr>
<td>PORT score of 4 or 5†‡</td>
<td>1204 (75.7)</td>
<td>4724 (70.9)</td>
<td>6024 (65.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Smoker</td>
<td>37 (2.3)</td>
<td>522 (7.8)</td>
<td>396 (4.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Nursing home resident‡</td>
<td>267 (16.8)</td>
<td>1388 (20.8)</td>
<td>2125 (23.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>State</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>California</td>
<td>392 (24.7)</td>
<td>3071 (46.1)</td>
<td>4712 (51.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Louisiana</td>
<td>404 (25.4)</td>
<td>541 (8.1)</td>
<td>857 (9.4)</td>
<td>.001</td>
</tr>
<tr>
<td>Florida</td>
<td>717 (45.1)</td>
<td>2654 (39.8)</td>
<td>2605 (28.5)</td>
<td>.001</td>
</tr>
<tr>
<td>Missouri</td>
<td>77 (4.8)</td>
<td>395 (5.9)</td>
<td>968 (10.6)</td>
<td>.001</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer or leukemia†‡</td>
<td>172 (10.8)</td>
<td>905 (13.6)</td>
<td>1161 (12.7)</td>
<td>.01</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>445 (28.0)</td>
<td>2067 (31.0)</td>
<td>2662 (29.1)</td>
<td>.009</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>340 (21.4)</td>
<td>1558 (23.4)</td>
<td>1967 (21.5)</td>
<td>.01</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>398 (25.0)</td>
<td>1724 (25.9)</td>
<td>2228 (24.4)</td>
<td>.09</td>
</tr>
<tr>
<td>End-stage renal disease</td>
<td>122 (7.7)</td>
<td>483 (7.3)</td>
<td>617 (6.8)</td>
<td>.27</td>
</tr>
<tr>
<td>HIV infection</td>
<td>70 (4.4)</td>
<td>348 (5.2)</td>
<td>327 (3.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Liver disease</td>
<td>26 (1.6)</td>
<td>143 (2.2)</td>
<td>169 (1.9)</td>
<td>.26</td>
</tr>
<tr>
<td>Stroke</td>
<td>207 (13.0)</td>
<td>935 (14.0)</td>
<td>1254 (13.7)</td>
<td>.56</td>
</tr>
<tr>
<td>Pneumococcal vaccine§</td>
<td>1292 (81.3)</td>
<td>377 (5.7)</td>
<td>74 (0.8)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: HIV, human immunodeficiency virus; PORT, Pneumonia Outcomes Research Team.

*Data are given as number (percentage) unless otherwise specified.
†On admission, calculated as described in Fine et al.21
‡Prior to hospital admission.
§Pneumococcal vaccination coded as “ever” vs “never or unknown.”

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We evaluated differences in influenza vaccine effect in population subgroups, both through graphical inspection of differences in mortality rates and incorporation of interaction terms and indicator variables into regression models. Crude in-hospital mortality increased for both vaccinated and unvaccinated individuals as PORT scores increased, but influenza vaccination was associated with reduced mortality for individuals with high (≥4) PORT scores as well as for those with lower scores. A non-significant linear trend was seen for increasing effectiveness by PORT class (P = .11). No statistical evidence was found to suggest that influenza vaccination was less effective in preventing death in individuals 65 years or older (P = .43). A history of influenza vaccination appeared to be more protective in the first and third influenza seasons under study (OR, 0.31; 95% CI, 0.21-0.46) compared with the second and fourth seasons (OR, 0.44; 95% CI, 0.28-0.69), which is consistent with the excellent match between available vaccine and circulating influenza strains in the former seasons. However, this difference was not statistically significant (P = .27) (Figure 2).

We performed exploratory analyses on the whether a record of current influenza vaccination has an impact on recorded adverse events other than in-hospital death. While the crude risks of respiratory failure (OR, 0.66; 95% CI, 0.49-0.87) and sepsis syndrome (OR, 0.52; 95% CI, 0.30-0.89) were reduced in individuals with a history of current influenza vaccination, no significant reduction in risk was seen under varying assumptions after adjustment for severity of illness, comorbidity, smoking status, and pneumococcal vaccination status. We found no evidence to suggest a decrease in the risk of other medical complications of hospitalization in individuals with current influenza vaccination.

The impact of influenza vaccination in preventing hospital admission related to influenza, pneumonia, and other medical conditions in at-risk populations remains controversial. However, an independent effect of vaccination in attenuating respiratory illness would benefit public health in and of itself. We have previously identified such a benefit with 23-valent polysaccharide pneumococcal vaccination, and we attempted to identify a similar effect associated with current influenza vaccination. Of note, our findings are consistent with those of Nordin et al, who found a larger reduction in mortality than in hospitalization in older adults vaccinated against influenza (35% to 61% reduction in mortality vs 19% to 24% reduction in hospitalization), which is consistent with protection against death in individuals who become sufficiently ill to warrant hospitalization despite vaccination.

We found that current influenza vaccination among individuals admitted to a hospital with CAP was associated with a diminished risk of in-hospital all-cause mortality, even after controlling for other factors likely to be associated with both vaccination and risk of mortality. The extent of this reduction ranged from a low of 22%, when individuals with unknown vaccination status were assumed to be vaccinated, to 43% if such individuals were excluded from the analysis. In other words, even if most or all individuals with unknown vaccine status were actually vaccinated (as may have been the case), we would still have identified a significant survival benefit associated with current influenza vaccination.

The mechanism of such an effect might be postulated to result from attenuation of influenza by an antibody specific for current circulating viral strains. Attenuation of influenza-related illness has been associated with vertical transmission of anti-influenza antibody from mothers to infants and appears to occur in humans reinfected with a viral strain to which they have been exposed previously.

Alternately, the effect identified here could represent a shift toward pneumonia caused by other less virulent pathogens. It has been suggested that infection with influenza viruses predisposes hosts to bacterial pneumonia caused by S pneumoniae, a mechanism that would be consistent with the usual coincidence of elevated influenza and pneumococcal activity in North America. However, the persistence of the protective effect of vaccination, even when analyses were restricted to the most ill individuals (ie, those with the highest PORT scores), suggests that factors other than attenuation of illness may also play an important role in this effect.

Given the large number of individuals in this cohort with unknown vaccine status, the protective effect of pneumococcal vaccination against in-hospital mortality...
ity,17,18 and the high frequency of covaccination in this cohort, it is also possible that the protective effect we attribute to influenza vaccination actually represents residual confounding by corecipient of pneumococcal vaccination. Such a possibility is not ruled out by the robustness of our findings in the face of sensitivity analyses related to individuals with unknown vaccine status. As in any observational study, residual confounding by other unmeasured subject characteristics is also possible.

Nonetheless, our data may provide a further rationalization for improved influenza vaccine coverage and may suggest an important new consideration in risk analytic models related to the rapid production and stockpiling of vaccine in the case of an influenza pandemic.39 In the United States, levels of both influenza and pneumococcal vaccine coverage remain below target levels for at-risk groups,13 and it might be postulated that informational vaccine coverage remain below target levels for at-risk groups in the United States, while years 2/4 are the 1999-2000 and 2001-2002 influenza seasons, while years 2/4 are the 2000-2001 and 2002-2003 influenza seasons. PORT indicates Pneumonia Outcomes Research Team.

While this study has numerous strengths, such as inclusion of individuals in community hospitals in the database, a large sample size, and verification of discharge diagnoses among individuals included in the database, it has important limitations as well. The potential impact of unknown vaccine status on study results has been mentioned in the "Results" section. Given the fact that our study was limited to individuals hospitalized with pneumonia, if vaccination status were correlated with both likelihood of hospitalization and risk of in-hospital mortality, it is possible that selection bias could have been introduced to the study.41 Indeed, it appears likely that vaccination would be most effective in the prevention of hospitalization in younger, more robust individuals who would be at decreased risk of mortality.42 In this case, selection bias would have resulted in the underestimation of the true protective effect of influenza vaccination with respect to in-hospital mortality.

Other limitations include the absence of microbiological data on hospitalized individuals, though definitive microbiological diagnosis of CAP remains notoriously difficult.43 In addition, we have no data on influenza vaccination in past seasons; because most current influenza A infections involve H3N2 viral strains, cross-immunity due to prior vaccination and infection may attenuate the beneficial effects of current influenza vaccination identified here.32,44,45

In summary, we found that a record of current influenza vaccination was associated with improved hospital survival among survivors in a large cohort of individuals admitted to a hospital with CAP. The finding of enhanced survival remained robust in the face of a variety of different assumptions regarding the status of individuals with unknown vaccine status. If confirmed, this finding represents an important additional benefit of enhanced influenza vaccination coverage in populations at risk for CAP.

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**Additional Information:** See the box at the top of this page for a listing of the 34 institutions that contributed data during 4 consecutive influenza seasons (November 1999–April 2003).

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**REFERENCES**


