

Prior Pneumococcal Vaccination Is Associated with Reduced Death, Complications, and Length of Stay among Hospitalized Adults with Community-Acquired Pneumonia

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Background. Vaccination with pneumococcal polysaccharide reduces the incidence of bacteremic pneumococcal disease in adults. We investigated the impact of prior pneumococcal vaccination on in-hospital mortality and the probability of respiratory failure among hospitalized adults with community-acquired pneumonia.

Methods. Consecutive individuals hospitalized with community-acquired pneumonia (diagnosed by *International Classification of Diseases, Ninth Revision, Clinical Modification* codes 480.0–487.0) at 109 community and teaching hospitals in the United States were identified using the Quality and Resource Management System, a database constructed by Tenet HealthCare to improve the quality of patient care. Vaccination status, comorbidities, and outcomes were abstracted by case managers concurrently with patient care. Associations between vaccination, survival, and respiratory failure were defined using multivariable logistic regression models.

Results. Of 62,918 adults hospitalized with community-acquired pneumonia between 1999 and 2003, 7390 (12%) had a record of prior pneumococcal vaccination. Vaccine recipients were less likely to die of any cause during hospitalization than were individuals with no record of vaccination (adjusted odds ratio [OR], 0.50; 95% confidence interval [CI], 0.43–0.59), even after adjustment for the presence of comorbid illnesses, age, smoking, and influenza vaccination and under varying assumptions about missing vaccination data. Vaccination also lowered the risk of respiratory failure (adjusted OR, 0.67; 95% CI, 0.59–0.76) and other complications and reduced median length of stay by 2 days, compared with nonvaccination ($P < .001$).

Conclusions. Prior vaccination against pneumococcus is associated with improved survival, decreased chance of respiratory failure or other complications, and decreased length of stay among hospitalized patients with community-acquired pneumonia. These observations reinforce current efforts to improve compliance with existing pneumococcal vaccination recommendations for adults.

Serious infections caused by *Streptococcus pneumoniae* are a major source of morbidity and mortality among all age groups in both the developed and the developing worlds [1–4]. *S. pneumoniae* is the most commonly identified bacterial pathogen in individuals with community-acquired pneumonia [5]. Recent population-based surveillance efforts suggest that invasive disease affects 23 individuals per 100,000 in the United States

each year, with rates 3 times higher in individuals >64 years old [1].

In the developed world, case-fatality rates associated with serious pneumococcal infections range from 1% in children to 10%–40% in older individuals [6–9]. Antibiotics and intensive care may have a limited role in reducing early mortality in patients with pneumococcal bacteremia [10, 11], and the emergence of high-level antibiotic resistance has raised concerns about the current and future effectiveness of antibiotic regimens [4, 12]. These factors make control of pneumococcal disease through vaccination an attractive prospect [13].

A 23-valent polysaccharide pneumococcal vaccine is currently advocated for older adults and for younger individuals with certain chronic medical conditions [14, 15], despite conflicting results of randomized con-

Received 24 August 2005; accepted 19 December 2005; electronically published 13 March 2006.

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Clinical Infectious Diseases 2006;42:1093–101

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1058-4838/2006/4208-0006\$15.00

trolled trials involving adults [16–22]. Observational data, such as those derived from the Group Health Cooperative Study [23] and from a large cohort study conducted in Stockholm County, Sweden [24, 25], suggest that vaccination may prevent invasive pneumococcal disease, which itself has a high case-fatality rate. Prevention of invasive pneumococcal disease is advantageous, even in the absence of pneumonia prevention [23].

Observational studies, however, may be difficult to interpret, because of the differences in pneumonia risk between individuals who are vaccinated and individuals who are not (the so-called confounding by indication [26]). At this time, clear-cut evidence that 23-valent pneumococcal vaccine reduces mortality in older adults is limited [17, 24, 27], and its use in at-risk groups remains well below the Healthy People 2010 target levels [28].

Tenet Healthcare Corporation is a hospital system that includes >100 acute care hospitals located in various communities throughout the United States. Since 1999, Tenet has systematically collected data on individuals hospitalized with community-acquired pneumonia as part of a systemwide quality-improvement initiative. Our objective was to use this database to evaluate the impact of prior pneumococcal vaccination on survival of individuals hospitalized with community-acquired pneumonia. This approach implicitly adjusts for differences in individual risk of pneumonia that might otherwise distort observed vaccine effects in cohort studies.

METHODS

Study population. Study subjects were individuals aged ≥ 18 years with community-acquired pneumonia diagnosed by *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes 480.0–487.0 and who were admitted to acute care hospitals operated by Tenet Healthcare. When >1 record was available for a single individual, only the first was used for analysis. Data from 109 teaching and community hospitals, located in 15 states, were available for evaluation. Most Tenet institutions are located in California, Texas, Louisiana, and Florida, but additional hospitals are located throughout the southeastern United States and in Nebraska, Missouri, and Pennsylvania [29].

Data on hospitalized individuals were collected as part of a systemwide quality-improvement initiative in 38 hospitals in 1999 (the “Partnership for Change”), and data collection was subsequently extended to all Tenet institutions. The program was designed to evaluate clinical outcomes and hospital performance for sentinel medical conditions, including community-acquired pneumonia and cardiovascular disease.

Data were collected by use of a computer-based, rapid-cycle data collection and feedback system with the Quality Assurance and Resources Management System. Primary data collection

was performed by specially trained nurse case managers, who are directly involved in patient care, by use of laptop computers. Data collection was integrated into the routine clinical duties of case managers and was performed concurrently with patient care. Validation of primary diagnoses occurred at the end of each month, when data were reconciled with discharge ICD-9-CM codes to ensure complete capture of cases as well as correct classification of primary diagnoses. Data collection and definitions were standardized across hospitals, with guidelines for clinical abstraction posted on the Tenet Healthcare system’s internal Web site. Training in standardized data collection methods was overseen by a full-time corporate education director.

Severity of pneumonia, vaccination status, and clinical outcomes. Data on age, sex, past medical history, nursing home residence, vital signs, clinical and radiographic findings, and laboratory values at hospital admission were collected routinely for all patients assigned ICD-9-CM codes consistent with community-acquired pneumonia. These data were sufficient for calculation of Pneumonia Outcomes Research Team (PORT) scores [30]. Briefly, the PORT score is a validated clinical prediction rule that permits risk stratification with regard to the likelihood of adverse outcomes in individuals with community-acquired pneumonia. Records of comorbid conditions not used for calculation of PORT scores but which themselves constitute an indication for pneumococcal vaccination (i.e., HIV infection, diabetes mellitus, and chronic obstructive pulmonary disease) were also available [14, 15].

Data on lifetime vaccination against *S. pneumoniae* and vaccination against influenza since the last influenza season were routinely collected by case managers as part of an effort to ensure that unvaccinated individuals receive appropriate immunizations before discharge from the hospital [31]. Vaccine status was derived from a variety of sources, which included communication with the patient’s primary care physician or other caregivers, 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 medical record. Vaccine status was recorded as “received,” “not received,” or “unknown.”

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. Case managers also recorded complications that occurred during hospitalization, including respiratory failure, sepsis syndrome, in-hospital myocardial infarction, acute renal failure, and upper gastrointestinal bleeding.

Statistical analysis. The baseline demographic characteristics and health status of individuals with prior pneumococcal vaccination, individuals without prior pneumococcal vaccina-

Table 1. Characteristics of study population, by pneumococcal vaccination status.

Characteristic	Vaccinated (n = 7390)	Unvaccinated (n = 14,585)	Unknown vaccination status (n = 40,943)	P
Age, mean years \pm SD	71.7 \pm 16.6	73.5 \pm 18.8	71.4 \pm 17.2	<.001
Female sex	3410 (46.1)	6790 (46.6)	18,743 (45.8)	.26
PORT score IV or V ^a	5732 (77.6)	10,285 (70.5)	30,107 (73.5)	<.001
Admitted to teaching hospital ^b	197 (2.7)	730 (5.0)	2629 (6.4)	<.001
Smoker	820 (11.1)	2213 (15.2)	5351 (13.1)	<.001
Nursing home resident ^c	1345 (18.2)	3095 (21.2)	9469 (23.1)	<.001
Comorbidities				
Cancer or leukemia	1031 (13.4)	2369 (16.2)	5574 (13.6)	.05
Chronic obstructive pulmonary disease	2250 (30.5)	4401 (30.2)	12,343 (30.2)	.87
Congestive heart failure	1591 (21.5)	3147 (21.6)	9173 (22.4)	.05
Diabetes mellitus	1877 (25.4)	3402 (23.3)	10,101 (24.7)	<.001
End-stage renal disease	549 (7.4)	1071 (7.3)	3095 (7.6)	.68
HIV infection	333 (4.5)	1086 (7.5)	1624 (4.0)	<.001
Liver disease	129 (1.8)	360 (2.5)	886 (2.2)	.002
Stroke	961 (13.0)	1930 (13.2)	5742 (14.0)	.009
Prior influenza vaccine ^d	5173 (70.0)	324 (2.2)	1249 (3.1)	<.001

NOTE. Data are no. (%) of individuals, unless otherwise indicated. PORT, Pneumonia Outcomes Research Team.

^a Score at admission, calculated as described elsewhere [30].

^b University-affiliated teaching hospitals in Los Angeles, New Orleans, Omaha, and Philadelphia were part of the Tenet HealthSystem network during the data collection period.

^c Before hospital admission.

^d During current or most recent influenza season.

tion, and individuals with unknown vaccine status were compared using χ^2 tests for categorical variables and 1-way analysis of variance for continuous variables [32]. 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 [33].

Crude and adjusted ORs for all-cause in-hospital death and other adverse outcomes in those with a documented history of prior pneumococcal vaccination were generated through construction of univariable and multivariable logistic regression models [34]. Multivariable models were adjusted for subjects' PORT scores, and additional covariates that were associated with likelihood of vaccination in the univariable analyses were added to multivariable models in a stepwise fashion and were retained when the *P* value was $\leq .20$ [35].

Heterogeneity of the effect of pneumococcal vaccination according to PORT scores and age was evaluated through incorporation of multiplicative interaction terms into regression models [34]. Heterogeneity of effects was evaluated using the Wald χ^2 test [36]. Because it has been hypothesized that factors contributing to early and late in-hospital deaths among individuals with severe pneumococcal disease are different [10, 37], we evaluated heterogeneity of the effect of vaccination depending on duration of hospitalization, through construction of Cox proportional hazards models, with hospitalization du-

rations of ≥ 1 , 3, and 5 days evaluated as possible time-varying covariates [38]. Proportionality of hazards was assessed using standard graphical methods.

We hypothesized that the designation of vaccine status as unknown might be correlated with subject characteristics or clinical outcomes. Therefore, we performed wide-ranging sen-

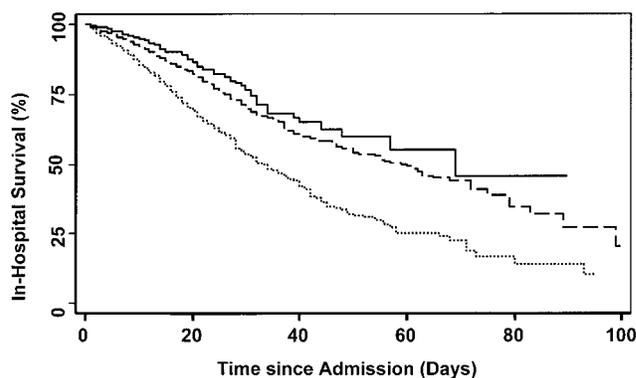


Figure 1. In-hospital survival among individuals admitted to hospitals with diagnosed community-acquired pneumonia. Differences in vaccination status were associated with significant differences in survival. The solid line represents individuals with known prior pneumococcal vaccination, the dashed line represents individuals with unknown vaccination status, and the dotted line represents unvaccinated individuals.

Table 2. Effect of prior pneumococcal vaccination on all-cause in-hospital mortality under varying assumptions about individuals with unknown vaccination status.

Variable	Adjusted OR (95% CI) for death			
	Subjects with unknown vaccine status excluded	Subjects with unknown vaccine status assumed unvaccinated	Subjects with unknown vaccine status assumed vaccinated	Unknown vaccine status replaced randomly
Pneumococcal vaccination	0.32 (0.26–0.39)	0.50 (0.43–0.59)	0.39 (0.36–0.42)	0.64 (0.59–0.68)
Influenza vaccination	0.77 (0.62–0.95)	0.79 (0.68–0.92)	1.29 (1.19–1.39)	0.79 (0.72–0.86)
PORT score	1.75 (1.66–1.84)	1.61 (1.56–1.66)	1.66 (1.60–1.71)	1.61 (1.56–1.67)
HIV infection	1.39 (1.16–1.66)	1.51 (1.33–1.71)	1.35 (1.14–1.54)	1.49 (1.31–1.69)
Smoking	0.72 (0.62–0.85)	0.83 (0.75–0.91)	0.83 (0.76–0.91)	0.83 (0.76–0.91)

NOTE. PORT, Pneumonia Outcomes Research Team.

sitivity analyses [39] in which individuals with unknown vaccine status were excluded, were assumed to be vaccinated, or had their vaccine status replaced randomly with a probability proportional to rates of vaccination among subjects with known vaccine status.

Microbiological data were not available for this data set. To evaluate whether the protective effect of pneumococcal vaccination was consistent with the known seasonality of pneumococcal disease [40], we incorporated sine and cosine terms into logistic regression models as described elsewhere [41]. These parameters were incorporated into interaction terms that were used to evaluate the possibility of seasonal differences in vaccine effect.

All statistical analyses were performed using the SAS, version 8.01 (SAS Institute), and Intercooled Stata, version 8.0 (Stata). The study was approved by the Institutional Review Board of Drexel University (Philadelphia, PA).

RESULTS

The database included records of 68,289 consecutive admissions for community-acquired pneumonia that occurred between September 1999 and December 2003. Of these, 603 were additional admissions of a single individual, and 4768 were admissions of subjects <18 years of age. A total of 62,918 records qualified for analysis.

Of study subjects, 12% had a record of pneumococcal vaccination before hospitalization, 23% were documented as unvaccinated, and the remainder of the study population had unknown vaccine status. Characteristics of study subjects by vaccination status are presented in table 1. Significant differences were seen between groups in age, prevalence of most comorbid conditions, receipt of influenza vaccine, smoking status, and history of nursing home residence. Individuals with prior vaccination had higher PORT scores than did individuals without prior vaccination.

Death due to any cause occurred during hospitalization in 4167 (7.6%) of the subjects. Individuals with documented prior

receipt of pneumococcal vaccine were less likely to die during hospitalization than were nonrecipients (crude OR, 0.29; 95% CI, 0.26–0.33) and individuals with unknown vaccine status (crude OR, 0.56; 95% CI, 0.50–0.64) (figure 1).

Multivariable models, constructed using different assumptions about individuals with unknown vaccine status, showed the survival advantage associated with prior pneumococcal vaccination to be robust, even after adjustment for possible confounding by severity of illness, comorbid medical conditions, age, and receipt of influenza vaccine. The adjusted OR for mortality among individuals with documented prior pneumococcal vaccination, relative to those without documentation of prior vaccination, was 0.50 (95% CI, 0.43–0.59) (table 2).

Crude in-hospital mortality increased for both vaccinated and unvaccinated individuals as PORT scores increased (figure 2). However, we found no evidence of differential effects of pneumococcal vaccination on survival in individuals with

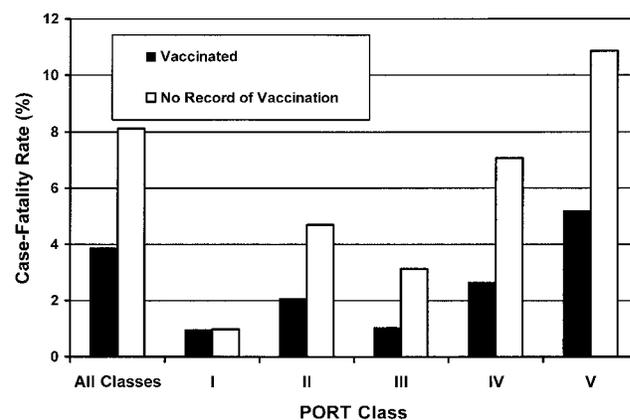


Figure 2. Crude in-hospital survival among individuals admitted for community-acquired pneumonia, stratified by Pneumonia Outcomes Research Team (PORT) classification [30]. For all but those with the lowest score (PORT class I), a record of prior pneumococcal vaccination was associated with reduced likelihood of in-hospital mortality.

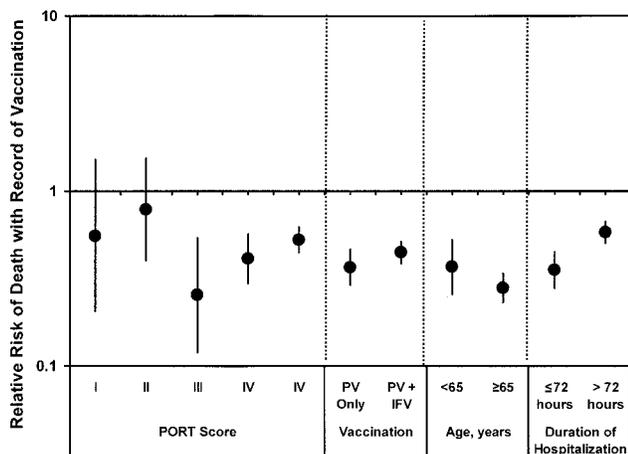


Figure 3. Subgroup analyses of adjusted relative risk of death among individuals with community-acquired pneumonia and a record of prior pneumococcal vaccination (PV). Heterogeneity of effects of vaccination was not seen with stratification by Pneumonia Outcomes Research Team (PORT) scores [30], record of influenza vaccination (IFV), or age, but vaccination appeared to be significantly more effective in reducing early death than in reducing late death. Relative risk was approximated by ORs for all analyses except for that of hospitalization duration, for which relative risk is represented by hazard ratios. Results are plotted on a common log scale.

higher PORT scores, although a nonsignificant trend toward heterogeneity in ORs was seen ($P = .13$). Similarly, we found no evidence to suggest that pneumococcal vaccination was less effective in preventing death in individuals ≥ 65 years old (adjusted OR, 0.29; 95% CI, 0.24–0.35), compared with individuals < 65 years old (adjusted OR, 0.35; 95% CI, 0.25–0.50; $P = .26$). Although both pneumococcal vaccination and influenza vaccination were independently associated with reduced risk of in-hospital mortality, the risk of mortality was not significantly

different for receipt of the 2 vaccines together (adjusted OR, 0.45; 95% CI, 0.39–0.52), compared with the receipt of only the pneumococcal vaccine (adjusted OR, 0.37; 95% CI, 0.29–0.47; $P = .16$) (figure 3).

Using a Cox proportional hazards model, we found that the adjusted effect of prior pneumococcal vaccination on mortality in the first 72 h of hospitalization was significantly greater than the effect on mortality later in the hospitalization ($P < .001$) (figure 3). This effect remained statistically significant under varying assumptions about individuals with unknown vaccine status (table 3).

We performed exploratory analyses on the impact of a record of prior pneumococcal vaccination on recorded adverse events other than in-hospital death. We found record of prior pneumococcal vaccination to be associated with a decreased risk of respiratory failure or acute respiratory distress syndrome (adjusted OR, 0.67; 95% CI, 0.59–0.76), tracheostomy during hospitalization (adjusted OR, 0.49; 95% CI, 0.33–0.73), acute renal failure (adjusted OR, 0.55; 95% CI, 0.46–0.65), sepsis syndrome (adjusted OR, 0.74; 95% CI, 0.61–0.90), and cardiac arrest during hospitalization (adjusted OR, 0.40; 95% CI, 0.29–0.57). Protection against respiratory or renal failure and sepsis syndrome remained statistically significant under varying assumptions about individuals with unknown vaccine status. Protection against tracheostomy was no longer significant when individuals with unknown vaccination status were assumed to be vaccinated. Prior vaccination did not reduce risk of in-hospital myocardial infarction, stroke, pulmonary embolism, or gastrointestinal bleeding (figure 4).

A history of prior pneumococcal vaccination was associated with decreased length of hospital stay when compared with unknown vaccine status or absence of pneumococcal vaccination (4.5 days for prior vaccination, compared with 5.5 days

Table 3. Cox proportional hazards model demonstrating effect of pneumococcal vaccination on relative hazard of death, by duration of hospitalization.

Variable	Adjusted hazard ratio (95%CI) for death			
	Subjects with unknown vaccine status excluded	Subjects with unknown vaccine status assumed unvaccinated	Subjects with unknown vaccine status assumed vaccinated	Unknown vaccine status replaced randomly
Pneumococcal vaccination and ≤ 72 -h hospitalization	0.23 (0.18–0.30)	0.36 (0.28–0.45)	0.49 (0.44–0.54)	0.59 (0.53–0.67)
Pneumococcal vaccination and > 72 -h hospitalization ^a	0.39 (0.34–0.46)	0.59 (0.51–0.67)	0.54 (0.50–0.58)	0.69 (0.63–0.75)
PORT class	1.57 (1.50–1.65)	1.48 (1.43–1.54)	1.52 (1.47–1.57)	1.49 (1.44–1.54)
HIV infection	1.19 (1.01–1.39)	1.24 (1.10–1.40)	1.13 (1.00–1.28)	1.22 (1.08–1.38)
Chronic obstructive pulmonary disease	0.95 (0.86–1.05)	0.93 (0.87–0.99)	0.92 (0.87–0.99)	0.93 (0.87–0.99)
Diabetes mellitus	0.91 (0.82–1.01)	0.83 (0.78–0.89)	0.84 (0.78–0.89)	0.83 (0.78–0.89)
Community hospital	1.43 (1.12–1.81)	1.32 (1.15–1.51)	1.24 (1.08–1.42)	1.30 (1.13–1.49)
Smoker	0.79 (0.68–0.91)	0.90 (0.82–0.99)	0.90 (0.82–0.99)	0.91 (0.83–1.00)

NOTE. PORT, Pneumonia Outcomes Research Team.

^a Coefficient for multiplicative interaction between pneumococcal vaccination and pneumococcal vaccination \times hospitalization time (either ≤ 72 h or > 72 h). The 95% CIs were calculated using parameter variance and covariance as described elsewhere [38].

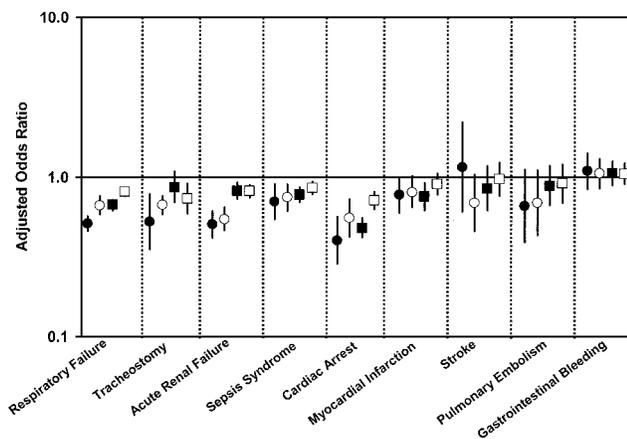


Figure 4. Adjusted ORs for record of complications of hospitalization, under varying assumptions about pneumococcal vaccination in individuals with unknown vaccination status. Shown are data with individuals with unknown status excluded (*blackened circles*), individuals with unknown status assumed to be unvaccinated (*open circles*), individuals with unknown status assumed to be vaccinated (*blackened squares*), and unknown status randomly replaced (*open squares*). Estimates were generated using logistic regression models that controlled for Pneumonia Outcomes Research Team (PORT) scores, concurrent influenza vaccination, other medical comorbidities, smoking status, and community hospital care, as appropriate. Results are plotted on a common log scale.

for unknown status and 6.5 days for nonvaccination; $P < .001$ for all pairwise comparisons by log-rank test). Adjusted alive-at-discharge rates for individuals with prior pneumococcal vaccination were higher than those for individuals without record of prior vaccination (adjusted hazard ratio, 1.05; 95% CI, 1.01–1.09) and remained significant regardless of the assumptions about individuals with unknown vaccine status.

When a cosine term was incorporated into regression models restricted to individuals with known vaccine status, we found evidence of seasonality of mortality for pneumonia ($P = .001$). The protective effect of pneumococcal vaccination also appeared to be seasonal in these models (for interaction between vaccination and cosine of month, $P = .01$) (figure 5), with the greatest protection against death afforded by vaccination during colder months, when pneumococcal disease is expected to be more prevalent [40]. However, this relationship was not robust when varying assumptions were made about individuals with unknown vaccination status.

DISCUSSION

We found record of prior pneumococcal vaccination to be associated with a 40%–70% reduction in risk of in-hospital death in a large cohort of consecutive individuals with community-acquired pneumonia who were admitted to community and teaching hospitals in disparate areas of the United States. Prior vaccination also appeared to reduce other adverse health out-

comes and length of stay. These effects remained statistically and clinically significant even after controlling for severity of illness, comorbid conditions, and other potential confounding variables and under varying assumptions about subjects with unknown vaccine status. These findings have important implications for the future enhancement of pneumococcal vaccine uptake in North America.

Our findings are consistent with the observation that polyvalent pneumococcal polysaccharide vaccine reduces bacteremic pneumococcal disease in adults [23, 25, 42] and with the reports of reduction in pneumonia-related mortality among vaccinated individuals in observational studies performed in Sweden and Austria [25, 43]. Pneumococcal bacteremia has high case-fatality rates, which have been noteworthy for their persistence despite decreased overall case-fatality rates for pneumococcal disease since the introduction of penicillin and other advances in medical care [10, 11, 44]. Elevated mortality resulting from pneumococcal bacteremia, despite an adequate host immune response and in the presence of antibiotic therapy, may result from release of cell-wall components by killed bacteria, which results in an inflammatory cascade that causes death in experimental models of pneumococcal disease [37]. Mechanistically, prevention of such a “cytokine storm” would be consistent with our finding that prior vaccination appeared to have the greatest effect on mortality during the first 72 h of hospitalization and could also explain the observed reduction in respiratory failure, sepsis syndrome, and renal failure [45–47]. It appears reasonable to posit that the reduced incidence of such complications could serve as a causal mechanism for the observed decrease in hospital stay for vaccinated individuals.

Our findings, if confirmed, will add an important dimension to the debate on application of pneumococcal vaccination in

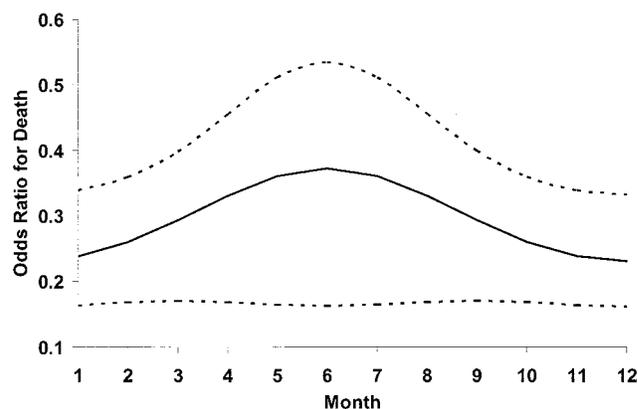


Figure 5. Seasonality of effect of prior pneumococcal vaccination on mortality, estimated using a logistic regression model with an interaction term based on the cosine of month. The observed effect of vaccination is greatest during months when invasive pneumococcal disease is most common in the United States [40].

adults [48] and could also enhance the accuracy of clinical prediction rules related to community-acquired pneumonia outcomes [30, 49]. Health economic analyses of pneumococcal vaccination in adults support current guidelines but have focused largely on the effectiveness of vaccination in reducing the incidence of pneumococcal disease, as opposed to changing the outcome of such disease [50, 51]. A marked reduction in death resulting from putative pneumococcal disease, as described here, suggests that improved compliance with existing recommendations for vaccination would save thousands of lives annually in the United States alone, whereas reductions in ventilatory support and length of hospital stay would counterbalance the societal cost of increased vaccination. For example, on the basis of the conservative assumption that half of the estimated 44,280 adults with invasive pneumococcal disease in 1998 [1] were unvaccinated, an average reduction in length of stay of 2 days for individuals hospitalized with invasive pneumococcal disease would save ~\$36 million annually in Medicare reimbursements alone [52].

Like any observational study, this study has limitations. It should be noted, however, that these are largely distinct from the limitations of previously published analyses of pneumococcal vaccine efficacy and effectiveness in adults. Inconsistencies in the reported effectiveness of pneumococcal vaccination in clinical trials in adults have been ascribed to a lack of statistical power [27, 42, 53], a limitation overcome by the large size of the cohort in the present study. The problem of so-called confounding by indication in observational studies (i.e., the receipt of vaccination by individuals at highest risk of disease [26]) is partially remedied by the fact that all subjects included in the study were, by definition, at risk of acquiring community-acquired pneumonia. Furthermore, stratification by risk level did not reveal important differences in vaccine effect between low-risk and high-risk individuals, and estimates of vaccine effectiveness were stable with adjustment for multiple potential confounders.

Our study was limited by incomplete information on vaccination status and by a lack of bacteriological data. However, estimates of vaccine effectiveness remained statistically significant after wide-ranging sensitivity analyses for missing vaccine data [39]. Although we lacked bacteriologic data on pneumonia etiology and on the presence of bacteremia, the inability to exclude pneumonia due to other etiologies probably biases our study toward a null effect for vaccine, because individuals with other types of pneumonia would not experience benefit from pneumococcal vaccination. Furthermore, the seasonal protective pattern detected here is consistent with the known epidemiology of invasive pneumococcal disease in the United States [40].

In summary, we studied a large cohort of individuals with community-acquired pneumonia. In this population, a history

of prior pneumococcal vaccination was associated with decreased risk of death, complications of hospitalization, and length of stay. Reductions in both early and late mortality were seen, and findings were not confounded by pneumonia risk (because all individuals had pneumonia) nor by propensity to receive vaccination. These findings are consistent with reduction in risk of bacteremic pneumococcal disease after vaccination [23, 42]. Although polyvalent protein-conjugate vaccines may ultimately prove to be more effective than polysaccharide vaccines for prevention of disease in adults [54], this study provides further evidence of the potential health and economic benefits of the current vaccine preparation and underlines the importance of current efforts to improve compliance with existing recommendations for 23-valent pneumococcal vaccine in adults [55].

Acknowledgments

We thank Drs. Robert Austrian, Joshua Metlay, and Huiling Zhang and 3 anonymous reviewers, for their many insightful comments related to the manuscript. We also thank Julia Mitina for her contributions to the construction and maintenance of the Quality Assurance and Resources Management System database.

Financial support. Tenet Healthcare Foundation (grant GFW 11595); National Institute of Occupational Safety and Health (R01-OH007489 to D.N.F.).

Potential conflicts of interest. J.D., C.K., and A.K. are employees of Tenet Healthcare Corporation. D.N.F. has received research support from Suturtek and has served as a consultant for Viropharma. E.A. has served as a consultant for Cubist Pharmaceuticals. K.A.S.: no conflicts.

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