The Health and Economic Benefits Associated With Pneumococcal Vaccination of Elderly Persons With Chronic Lung Disease

Kristin L. Nichol, MD, MPH; Leslie Baken, MD; Janet Wuorenma, RN, BSN; Andrew Nelson, MPH

Background: More than 50% of the elderly population has not received pneumococcal vaccination. Uncertainty regarding the benefits of immunization, particularly for noninvasive disease, may contribute to the underuse of pneumococcal vaccine.

Objective: To assess the health and economic benefits associated with pneumococcal vaccination.

Methods: We conducted a 2-year retrospective cohort study among all elderly members of a staff-model managed care organization who had a baseline diagnosis of chronic lung disease. The study outcomes were assessed over 2 years, from November 15, 1993, through November 14, 1995, and included hospitalizations for pneumonia and influenza, death, and hospitalization costs. Using administrative data, we compared these outcomes for vaccinated and unvaccinated subjects using multivariate models to control for subjects' baseline demographic and health characteristics. The additive benefits of combined influenza and pneumococcal vaccination were also assessed for the 2 influenza seasons included in the study.

Results: There were 1898 subjects. Pneumococcal vaccination was associated with significantly lower risks for pneumonia hospitalizations (adjusted risk ratio [RR], 0.57; 95% confidence interval [CI], 0.38-0.84; $P = .005$) and for death (adjusted RR, 0.71; 95% CI, 0.56-0.91; $P = .008$). For the control outcome of all nonpneumonia hospitalizations, rates did not differ significantly between the 2 groups (adjusted RR, 0.91; 95% CI, 0.77-1.07; $P = .24$). During the influenza seasons included in the study, the benefits of pneumococcal and influenza vaccinations were additive, with an adjusted RR of 0.28 (95% CI, 0.14-0.58; $P<.001$) for the number of hospitalizations for pneumonia and influenza among persons who had received both vaccinations compared with those who had received neither and an adjusted odds ratio of 0.18 (95% CI, 0.11-0.31; $P<.001$) for death. Over the 2-year outcome period, pneumococcal vaccination was also associated with direct medical care cost savings.

Conclusions: Pneumococcal vaccination of elderly persons with chronic lung disease was associated with fewer hospitalizations for pneumonia, fewer deaths, and direct medical care cost savings.

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From the Veterans Affairs Medical Center and the University of Minnesota Medical School, Minneapolis (Dr Nichol); and HealthPartners and Group Health Research Foundation, Bloomington, Minn (Dr Baken and Ms Wuorenma and Mr Nelson). Dr Baken is now with Park Nicollet Clinic and HealthSystem Minnesota, St Louis Park, Minn.

*S*TREPTOCOCCUS PNEUMONIAE is a major cause of morbidity and mortality, causing 50 000 cases of bacteremia, 500 000 cases of pneumonia, and 40 000 deaths each year in the United States.[1] Vaccination is recommended as the most cost-effective means of preventing invasive disease for the elderly and others who are at increased risk for serious pneumococcal infections and their complications.[1-5] Despite these recommendations, pneumococcal vaccine is underused. In the United States, more than 50% of the elderly population and other high-risk persons have not been immunized.[6,7]

Uncertainty regarding the benefits of vaccination may contribute to low immunization rates. Previous studies, including clinical trials,[8] indirect cohort studies,[9] and case-control studies,[10-12] with one exception,[13] have documented the effectiveness of pneumococcal vaccine in preventing invasive pneumococcal diseases, such as bacteremia and meningitis. However, data regarding the effectiveness of this vaccine in reducing other, more common manifestations of pneumococcal disease, such as pneumonia, have been inconclusive for high-risk groups,[1] leading some to question recommendations for routine immunization.[14,15] Prelicensure trials in young, healthy South African gold miners,[16,17] US military recruits,[18] and residents of long-term care facilities[19] all showed significant reductions in episodes of pneumonia, but the applicability of these studies to high-risk populations currently targeted for vaccination is questionable. Trials in the United States and Canada using licensed 14-valent vaccines have not shown benefit from vaccination in either low-risk or high-risk groups.[20-23] A recent trial from Sweden that

SUBJECTS AND METHODS

SETTING

Group Health, Bloomington, Minn, is a staff-model health maintenance organization that is affiliated with Health Partners, a vertically integrated health care system. Group Health serves more than 250 000 members in the Minneapolis–St Paul area with its 21 clinics and more than 350 salaried physicians. In 1989, Group Health piloted a modified version of the Minneapolis Veterans Affairs Medical Center's Influenza Vaccination Program in 2 of its clinics.[27] This program was expanded to all of the Group Health staff-model clinics in 1990. This highly successful program has achieved influenza vaccination rates in excess of 60% for its elderly members and has been associated with improved health and cost savings for this high-risk group.[28,29] The essential elements of this program include standing orders for nurses, walk-in clinics, and informational/publicity mailings to high-risk patients. This program has been expanded to include the provision of pneumococcal vaccinations for high-risk members.

SUBJECTS

All members of the staff-model health maintenance organization who were aged 65 years or older on October 1, 1993, who had a diagnosis of chronic lung disease (*International Classification of Diseases, Ninth Revision–Clinical Modification* [*ICD-9-CM*] codes 491-496 or 500-518) during the preceding 12 months (October 1, 1992, through September 30, 1993), who were alive on the first day of the outcome period, and who were continuously enrolled throughout the 12-month baseline period were included in the cohort.

DATA COLLECTION AND STUDY OUTCOMES

This study is one of several projects that will evaluate the impact of vaccine-preventable diseases in this cohort, and we have previously reported on the benefits of influenza vaccination in this cohort.[30] All data for this study, including vaccination status, were obtained from the linked administrative databases of the health maintenance organization using methods adapted from those used for serial, single-season cohort studies that assessed the effectiveness of influenza vaccination among all elderly members of the health plan.[28,29] Baseline characteristics were collected from October 1, 1992, through September 30, 1993, and included age, sex, and the number of physician visits. Other information that was collected included whether the subject had comorbid medical conditions reflected by diagnoses of heart disease (*ICD-9-CM* codes 393-398, 410-414, 425, or 428-429), diabetes mellitus (*ICD-9-CM* code 250), chronic renal disease (*ICD-9-CM* codes 581-582 or 585 with the *Current Procedural Technology, 4th Revision* [*CPT-4*] code for dialysis 39.95), vasculitis/rheumatologic disease (*ICD-9-CM* codes 446, 710, or 714), dementia/stroke (*ICD-9-CM* codes 290-294, 331, 340-341, 348, or 438), liver disease (*ICD-9-CM* code 571), cancer (*ICD-9-CM* codes 140-208), and whether they had a previous hospitalization for pneumonia (including influenza) (*ICD-9-CM* codes 480-487). Because of practical constraints, we were only able to ascertain pneumococcal vaccination status (*CPT-4* code 907.32) back to January 1, 1988. Protection following initial vaccination may last for up to 9 years or longer.[1,9] However, in the elderly, antibody levels decline within 5 to 10 years following vaccination.[1] This decline in antibody levels may also be associated with declining protection. A case-control study has suggested that protection may be reduced after 6 years.[11] The period we used to assess pneumococcal vaccination status is consistent with a 6- to 9-year duration of protection following initial vaccination. Influenza vaccination status (*CPT-4* code 907.24) was determined for each of the 2 vaccination periods included in the study influenza season included in the study (October 1, 1993, through December 31, 1993, and October 1, 1994, through December 31, 1994).

The study outcomes included hospitalizations for pneumonia (including influenza, *ICD-9-CM* codes 480-487) and deaths from all causes. We also compared hospitalization costs for pneumonia and influenza in the 2 groups. Hospitalization costs reflected billed charges adjusted by the Medicare cost-to-charge ratio for urban Minnesota hospitals.[31] These costs were also used in an economic analysis that assessed the net direct costs (savings) associated with vaccination in this cohort. A control outcome of all non-pneumonia hospitalizations was also evaluated to test the adequacy of the multivariate models. We hypothesized that

assessed the effectiveness of the 23-valent vaccine among persons previously hospitalized for community-acquired pneumonia also failed to demonstrate a reduction in subsequent pneumococcal pneumonias among vaccine recipients.[24] These modern trials have included subjects with varying levels of risk for serious complications from pneumococcal disease. Most of the studies with negative results lacked sufficient statistical power to detect differences between the treatment groups.[1] Two contemporary trials have had positive results. One was a nonblinded study conducted among residents of geriatric hospitals in France, in whom vaccination was associated with a 77% reduction (95% confidence interval [CI], 51%-89%) in episodes of pneumonia.[25] The other was conducted among elderly persons in Finland.[26] The overall results of the latter trial were negative, but a subgroup analysis among increased-risk and high-risk subjects demonstrated a vaccine effectiveness of 57% (95% CI, 6%-82%).

We conducted this cohort study to further assess and clarify the association of pneumococcal vaccination with hospitalizations for pneumonia, influenza, and death. We also evaluated the economic implications of vaccination. To enhance the statistical power of the study, we selected a group at particularly high risk for the study outcomes—elderly persons with chronic lung disease.

RESULTS

Of 1898 subjects, 1280 (67%) had received a pneumococcal vaccination. This included 843 (44%) who received a pneumococcal vaccination prior to November 15, 1993, and an additional 437 (23%) who received a

the hospitalization rates should not differ significantly between the groups for this outcome.

The study outcome period was from November 15, 1993, through November 14, 1995. Outcomes were assessed according to their occurrence during influenza seasons or interim periods spanned by the 2-year outcome period. The influenza seasons were from November 15, 1993, through March 30, 1994, and from November 15, 1994, through March 30, 1995. These dates were selected based on data from the Minnesota Department of Health influenza surveillance program.[32,33] The interim periods were from April 1, 1993, through November 14, 1993, and from April 1, 1994, through November 14, 1994.

STATISTICAL ANALYSIS

Analysis of variance and χ^2 tests for multiple proportions were used to compare baseline status with pneumococcal vaccination status (ie, vaccinated prior to the first day of the outcome period [November 15, 1993], vaccinated during the outcome period, and never vaccinated). Multivariate models were used to compare the risks for the study outcomes for vaccinated and unvaccinated subjects while controlling for covariates and potential confounders (SAS version 6.12; SAS Institute, Cary, NC). Cox proportional hazards regression was used to compare the risk of death over the entire 2-year outcome period for vaccinated and unvaccinated subjects, while logistic regression with repeated measures was used to assess the additive effects of influenza and pneumococcal vaccinations in reducing the risk of death during the influenza seasons. Poisson regression with repeated measures was used to compare the number of hospitalizations in the 2 groups. Normal regression with repeated measures was used to compare the costs per hospitalization episode in the groups. Because the frequency distribution of costs was skewed, we used the natural logarithm of costs in that model. Vaccination status was included in all models as a time-dependent covariate to accommodate subjects whose vaccination status changed during the outcome period. Age (dichotomized as <80 vs ≥80 years), sex, and pneumococcal vaccination status were included in all models. Other variables were included in the models using stepwise selection procedures if $P<.1$. All variables listed in **Table 1** were considered for each model. For the Cox proportional hazards regression, subjects were censored when they disenrolled from the health plan. The logistic, Poisson, and normal regression analyses were adjusted for the numbers of months of follow-up available for each subject. In addition, for the repeated-measures analyses that spanned the entire 2-year outcome period, year (first vs second) and season (influenza vs interim) were also included in the models.

The economic analysis assumed the societal perspective. Net costs were calculated as follows[34]:

$$\text{Net Costs (Savings)} = \text{Costs}_{(Vaccination)}$$
$$+ \text{Costs}_{(Medical\ Care\ for\ Adverse\ Effects)}$$
$$- \text{Costs}_{(Hospitalizations\ Averted)}$$

The cost of medical care for adverse effects is equal to the incidence of adverse effects requiring medical attention multiplied by the cost of a provider visit. The cost of hospitalizations averted is equal to the 2-year cumulative incidence of hospitalization among unvaccinated persons multiplied by the effectiveness of vaccination multiplied by the costs per episode of hospitalization. The incidence of hospitalizations and the costs per hospitalization were taken from the study data. Data on the costs of vaccination and the incidence and costs of adverse effects caused by vaccination were derived from other sources. For the costs of vaccination, we used the Medicare reimbursement rate for pneumococcal vaccine and its administration.[35] For the incidence of adverse effects following vaccination that require medical attention, we used data from a recently reported large, quasi-experimental study of initial and repeated vaccination among elderly and high-risk persons.[36] For the costs of a physician visit for adverse events caused by vaccination, we used the average cost of a brief physician visit for an established patient for the health care plan. In addition to calculating base case costs, we also conducted sensitivity analyses for the worst case (least favorable to vaccination) and best case (most favorable to vaccination) combinations of parameter estimates across a plausible range of values for each parameter. Because the worst case and best case scenarios may represent unlikely extremes, we also conducted probabilistic sensitivity analyses using Monte Carlo simulation[37] (@RISK, Windows version, July 1997; Palisade Corp, Newfield, NY) to estimate a 95% probability interval for the base case estimate of net costs. All costs are in 1999 dollars and are presented both as net costs per 1000 persons vaccinated and as net costs per person vaccinated.

pneumococcal vaccination after that date. At baseline, vaccinated subjects were younger than unvaccinated subjects (Table 1). They were also less likely to have a diagnosis of heart disease, stroke/dementia, or cancer or to have a history of pneumonia; subjects in this group were more likely to have received an influenza vaccination for the 1993-1994 influenza season.

Over the 2-year outcome period, there were 174 hospitalizations for pneumonia and influenza, 1477 hospitalizations for all nonpneumonia conditions, and 275 deaths. The observed 2-year cumulative incidence rates for pneumonia and influenza hospitalizations were 138 hospitalizations per 1000 unvaccinated persons and 70 hospitalizations per 1000 vaccinated persons. Pneumococcal vaccination was associated with a 43% reduction (adjusted risk ratio [RR], 0.57; $P = .005$) in the number of hospitalizations for pneumonia and influenza and a 29% reduction (adjusted RR, 0.71; $P = .008$) in the risk for death from all causes (**Table 2**). For the control outcome of nonpneumonia hospitalizations, the rates did not differ significantly between the 2 groups (adjusted RR, 0.91; 95% CI, 0.77-1.07; $P = .24$).

During the 2 influenza seasons included in the study, the effects of influenza vaccination were additive to those of pneumococcal vaccination. Among persons who had received both vaccinations, there was a 72% reduction (adjusted RR, 0.28; 95% CI, 0.14-0.58; $P<.001$) in the number of hospitalizations for pneumonia and influenza and an 82% reduction (adjusted odds ratio [OR], 0.18; 95% CI, 0.11-0.31; $P<.001$) in the risk of death when compared with those who had received neither vaccination. There was no evidence for interaction between the 2 vaccinations for either outcome ($P = .96$ and $P = .59$, respectively).

Table 1. Baseline Characteristics of Study Subjects According to Pneumococcal Vaccination Status*

	Vaccinated Before 11/15/93 (n = 843)	Vaccinated After 11/15/93 (n = 437)	Not Vaccinated (n = 618)	P
Age, y				
Mean ± SD	73.6 ± 5.4	74.1 ± 5.2	74.9 ± 6.7	<.001
Median (25th-75th percentile)	72.6 (69.8-76.3)	72.7 (69.1-76.4)	73.7 (69.8-78.8)	
Male, %	50.5	49.9	45.6	.16
Comorbid conditions, %				
Heart disease	32.6	35.5	40.5	.008
Diabetes	16.7	14.6	19.1	.16
Stroke/dementia	5.3	3.7	8.1	.007
Chronic renal disease	4.3	2.7	3.9	.40
Rheumatologic disease	3.1	2.3	4.2	.21
Cancer	14.7	16.0	23.5	<.001
Liver disease	0	0.7	0.8	.04
History of pneumonia, %	17.3	14.2	20.4	.03
Influenza vaccination, %	80.3	78.5	56.0	<.001
Physician visits, No.				
Mean ± SD	18.2 ± 13.1	17.3 ± 11.8	18.0 ± 14.1	.52
Median (25th-75th percentile)	15.0 (9.0-24.0)	15.0 (10.0-22.0)	15.0 (8.0-26.0)	

Baseline diagnoses and resource utilization values are for the 12-month period from October 1, 1992, through September 30, 1993.

Table 2. Reduced Risk of Hospitalization and Death Over 2 Years Associated With Pneumococcal Vaccination of Elderly Persons With Chronic Lung Disease*

Outcome	Risk Ratio (95% CI)	P
Hospitalizations for pneumonia and influenza	0.57 (0.38-0.84)	.005
Death	0.71 (0.56-0.91)	.008

Risk ratios have been adjusted according to the multivariate models described in the "Methods" section. CI indicates confidence interval.

For persons who had at least one hospitalization for pneumonia and influenza, the costs per hospitalization episode were not significantly different between vaccinated and unvaccinated subjects (cost ratio, 0.80; 95% CI, 0.57-1.13; P = .21). Because these costs were similar between the study groups, further economic analyses used costs per hospitalization episode for all persons combined. The base case values used to calculate net costs, along with their sources and the ranges of values used in the sensitivity analyses, are shown in **Table 3**, while the cost savings for the base, best, and worst cases associated with vaccination are shown in **Table 4**. In the base case, pneumococcal vaccination was associated with net cost savings over 2 years of $293 689 per 1000 persons vaccinated or $294 per person vaccinated. The results of the sensitivity analyses showed that vaccination was even more cost-saving in the best case scenario and was still cost-saving even in the worst case. After 5000 simulations using the Monte Carlo simulation approach, the 95% probability interval for the average cost savings was found to be narrower than the range from best case to worse case; 95% of the time, the estimated 2-year cumulative cost savings fell between $113 and $512 per person vaccinated.

COMMENT

Recommendations from the Advisory Committee on Immunization Practices for the prevention of pneumococcal disease emphasize the effectiveness of vaccination for preventing invasive or bacteremic disease in the elderly and others with high-risk conditions.[1] Our findings suggest that the benefits of vaccination among elderly persons with chronic lung disease may also include the prevention of the more common outcome of serious pneumococcal disease—hospitalization for pneumonia. In our study, pneumococcal vaccination was associated with a 43% reduction in hospitalizations for pneumonia and a 29% reduction in mortality. Vaccination was also cost-saving.

Previous case-control and indirect cohort studies have demonstrated that pneumococcal vaccination of persons with risk conditions, such as chronic lung disease, is associated with a reduction in bacteremic disease.[9-11] Two small clinical trials, each with fewer than 200 subjects, were conducted among persons with chronic pulmonary disease.[22,23] Both trials failed to demonstrate benefits from vaccination in reducing pneumonia hospitalizations; these studies had small numbers of subjects and therefore had insufficient power to detect differences between the groups. One larger trial of 2295 veterans aged 55 years and older included 539 subjects with chronic pulmonary disease.[21] This study with negative results also had inadequate power. Our study extends these previous observations. We had a large number of subjects and high event rates, resulting in adequate power to detect an association between vaccination and a reduction in hospitalizations for pneumonia.

The reduction in mortality associated with pneumococcal vaccination in our study was substantial. These findings suggest that pneumococcal disease may be directly or indirectly responsible for a large percentage of deaths observed in this high-risk group. A recent meta-analysis of randomized, controlled trials did not find evidence for a significant reduction in mortality in the studies reviewed.[8] However, our study population differed in size and risk from most of those previously studied. Findings of similar reductions in mortality have been observed with influenza vaccination of the elderly[28,29,38,39]

Table 3. Variables and Assumptions Used in Cost Models

Variable	Base Case (Range)
Cost of vaccine and its administration, $*	15.55 (15.55-31.10)
Incidence of adverse effects requiring physician visits following vaccination†	2 per 1000 (1-3 per 1000)
Cost of a provider visit for adverse effects following vaccination, $‡	50 (50-100)
2-Year incidence of hospitalization for pneumonia and influenza among unvaccinated persons§	138 per 1000 (± 25%)
Cost per episode of hospitalization for pneumonia and influenza, $‖	5213 (3362-7481)
Effectiveness of vaccination in reducing hospitalizations for pneumonia and influenza, %¶	43 (15-62)

*The base case represents the 1999 Medicare reimbursement rate for pneumococcal vaccine and its administration.[35]

†The base case adapted from Jackson et al.[36]

‡The base case represents the 1999 cost of a brief physician office visit for an established patient (M. Goodman, HealthPartners Research Foundation, personal communication, April 1999).

§The base case is from the study data.

‖From the study data: median (25th-75th percentiles) costs per hospitalization episode adjusted by the Medicare cost-to-charge ratio[31] and adjusted to 1999 dollars using the medical care component of the Consumer Price Index (US Bureau of Labor Statistics).

¶Point estimate (95% confidence interval) from the study data. The values are adapted from Table 2; vaccine effectiveness equals 1 minus the risk ratio.

Table 4. Two-Year Cumulative Cost Savings Associated With Pneumococcal Vaccination

	Base Case*	Best Case†	Worst Case‡
Vaccination costs, $ per 1000 persons vaccinated			
Vaccine and its administration	15 550	15 550	31 100
Medical care for adverse effects	100	50	300
Cumulative, 2-year hospitalization costs (savings), $ per 1000 persons vaccinated	(309 339)	(800 114)	(52 042)
Cumulative, 2-year net costs (savings)			
$ per 1000 persons vaccinated	(293 689)	(784 514)	(20 642)
$ per person vaccinated§	(294)	(784)	(21)

*The average cost savings.

†Net costs with the combination of values (Table 3) most favorable to vaccination.

‡Net costs with the combination of values (Table 3) least favorable to vaccination.

§Based on Monte Carlo simulation, the 95% probability interval for the cumulative 2-year net costs (savings) per person is $113 to $512.

and in pediatric populations with the initiation of antimicrobial treatment of pneumonia.[40] This phenomenon has been described as a spillover benefit—that is, an overall effect greater than the attributed proportional contribution of pneumonia to total mortality in this population.[40] The pathophysiological basis for the mortality benefit observed in our population is not clear and warrants further investigation.

Pneumococcal vaccination in our study was associated with direct medical care cost savings. While our point estimate of cost savings is imprecise, our findings are consistent with what others have also observed—that pneumococcal vaccination is cost-effective and even cost-saving.[5,41] Certainly, pneumococcal vaccination compares favorably with and in many cases is more cost-effective than other preventive and therapeutic interventions.[42,43]

High-risk groups targeted for immunization are similar for influenza and pneumococcal vaccines.[1,44] The complications of each include hospitalizations for pneumonia. Our findings also illustrate the additive health benefits that can be achieved at a population level through the use of both vaccinations.

A serologic prevalence study from the Centers for Disease Control and Prevention has shown that the efficacy of pneumococcal vaccination in preventing bacteremic or invasive disease is similar among several risk groups, including persons with chronic pulmonary disease, coronary vascular disease, congestive heart failure, or diabetes mellitus and persons 65 years and older who are immunocompetent.[9] Whether the findings from our study can be generalized to other high-risk populations is unclear. Given the inconclusive nature of previous studies of this vaccine, we urge caution in applying our results to other high-risk groups.

The strengths of our study include the use of the cohort design, the strongest of all observational study designs[45] and the inclusion of a large, unselected group of high-risk subjects. The persons included in our cohort had a risk for hospitalization from pneumonia or influenza that was 3.5 times greater than that of elderly members of the managed care organization who did not have chronic lung disease (K.L.N., unpublished data, October 1998). Increased rates of hospitalization from pneumonia and influenza during influenza seasons among persons with chronic lung disease have also been observed in other studies.[46-48] These high event rates added to the power of our study. Because of the successful efforts of Group Health to immunize its members, we also had large numbers of vaccinated subjects in the cohort.

There are, however, important limitations of our study. Despite our efforts to adjust for important covariates and potential confounders, it is possible that we failed to measure and adjust for important differences between the 2 study groups. This is particularly of concern when there are significant differences in baseline characteristics between the groups, as observed in our study.[49] The similar rates of hospitalization between the 2 groups for the control outcome of all nonpneumonia conditions, however, suggest that our adjustment methods functioned fairly well. This study was not a randomized trial, however; the results should be interpreted with caution. Misclassification of pneumococcal vaccination status may also have influenced our results, especially in failure to capture immunization status. Over 90% of elderly members of this managed care organization who have received a pneumococcal vaccination have been immunized at a health plan site.[50] Furthermore, Group Health has encouraged accurate and complete documentation of influenza and pneumococcal vaccination status for its members for a number of years. Nevertheless, misclassification undoubtedly occurred and likely would have been in the direction of classifying vaccinated subjects as unvaccinated. This type of bias, if present, probably diminished our estimates of vaccine effectiveness.

CONCLUSIONS

Pneumococcal vaccination is a covered benefit for Medicare beneficiaries, and routine immunization of all senior citizens is recommended by the Advisory Committee on Immunization Practices as a cost-saving method for the prevention of invasive disease. Elderly persons with chronic lung disease may experience additional benefits from pneumococcal vaccination, including fewer hospitalizations for pneumonia and fewer deaths from all causes.

Corresponding author: Kristin L. Nichol, MD, MPH, Medicine Service (111), Veterans Affairs Medical Center, 1 Veterans Dr, Minneapolis, MN 55417 (e-mail: nicho014 @tc.umn.edu).

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