ORIGINAL ARTICLE

Effectiveness of Pneumococcal Polysaccharide Vaccine in Older Adults

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ABSTRACT

BACKGROUND

Streptococcus pneumoniae is the chief cause of pneumonia in older adults, but it remains unclear whether use of the pneumococcal polysaccharide vaccine alters the overall risk of community-acquired pneumonia. In a large population of older adults, we assessed the effectiveness of the pneumococcal vaccine.

METHODS

In this retrospective cohort study, 47,365 Group Health Cooperative members 65 years of age or older were assessed over a three-year period. The primary outcomes were hospitalization because of community-acquired pneumonia (validated by chart review), pneumonia in patients who were not hospitalized ("outpatient pneumonia," determined from administrative data sources), and pneumococcal bacteremia. The association between pneumococcal vaccination and the risk of each outcome was evaluated by means of multivariate Cox proportional-hazards models, with adjustment for age, sex, nursing-home residence or nonresidence, smoking status, medical conditions, and receipt or nonreceipt of influenza vaccine.

RESULTS

During the study period, 1428 cohort members were hospitalized with community-acquired pneumonia, 3061 were assigned a diagnosis of outpatient pneumonia, and 61 had pneumococcal bacteremia. Receipt of the pneumococcal vaccine was associated with a significant reduction in the risk of pneumococcal bacteremia (hazard ratio, 0.56; 95 percent confidence interval, 0.33 to 0.93) but a slightly increased risk of hospitalization for pneumonia (hazard ratio, 1.14; 95 percent confidence interval, 1.02 to 1.28). Pneumococcal vaccination did not alter the risk of outpatient pneumonia (hazard ratio, 1.04; 95 percent confidence interval, 0.96 to 1.13) or of any case of community-acquired pneumonia, whether or not it required hospitalization (hazard ratio, 1.07; 95 percent confidence interval, 0.99 to 1.14).

CONCLUSIONS

These findings support the effectiveness of the pneumococcal polysaccharide vaccine for the prevention of bacteremia, but they suggest that alternative strategies are needed to prevent nonbacteremic pneumonia, which is a more common manifestation of pneumococcal infection in elderly persons.

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Community-acquired pneumonia results in an estimated 350,000[1] to 620,000[2] hospitalizations each year among persons 65 years of age and older in the United States, and in that group the category of pneumonia and influenza is the fifth leading cause of death.[3] *Streptococcus pneumoniae* is the most common cause of community-acquired pneumonia in older adults,[1,4-6] and a vaccine that protected against pneumococcal pneumonia could reduce the risk of community-acquired pneumonia in this group. Since the majority of cases of pneumococcal pneumonia are not associated with bacteremia,[6] an effect of vaccination against community-acquired pneumonia would probably be evident only if the vaccine provided protection against nonbacteremic pneumococcal infections.

A retrospective cohort study of 1898 older adults with chronic lung disease showed that the 23-valent pneumococcal polysaccharide vaccine was associated with a significant reduction in the risk of hospitalization because of pneumonia.[7] In contrast, multiple prospective clinical trials of pneumococcal polysaccharide vaccines in older adults have, with one exception,[8] failed to document a reduction in the risk of pneumonia in the vaccinated group.[9-13] However, five of those studies[8-11,13] evaluated fewer than 1500 vaccinated subjects and therefore had a limited ability to detect a true effect of the vaccine.

It is therefore not clear whether the 23-valent pneumococcal polysaccharide vaccine reduces the risk of pneumonia in older adults. This is an important question, because other pneumococcal vaccine formulations, such as the protein conjugate vaccine now recommended for universal immunization of infants, may be more effective against nonbacteremic pneumococcal pneumonia.[14] The emergence of antibiotic-resistant strains of *S. pneumoniae* further increases the importance of the prevention of pneumococcal infections.[15,16] To evaluate the effectiveness of pneumococcal polysaccharide vaccine against community-acquired pneumonia, as well as the more specific outcome of pneumococcal bacteremia, we conducted a population-based retrospective cohort study of more than 47,000 persons 65 years of age or older.

METHODS

STUDY COHORT

The study population consisted of members of the Group Health Cooperative, a health maintenance organization (HMO) in Washington State, who were at least 65 years of age on March 1, 1998 (the date of the start of the study) and who had been enrolled for at least one year before that date. Cohort members were followed until death, disenrollment from the HMO, or the end of the study on February 28, 2001, whichever came first. The institutional review board of Group Health Cooperative approved the study and certified that it met the criteria for a waiver of the requirement to obtain informed consent.

SOURCES OF DATA AND DEFINITIONS

Sources of Data

The Group Health Cooperative maintains administrative data bases that record immunizations, laboratory tests, radiographic procedures, medication prescriptions, and diagnoses associated with outpatient visits and hospitalizations, which are coded according to the *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM).[17] Each member also has a paper medical record that contains copies of dictated hospital admission and discharge summaries, notes on outpatient and emergency room visits, and results of laboratory tests.

Covariates

Coronary artery disease, chronic lung disease, diabetes mellitus, dementia or stroke, and immunosuppression were defined on the basis of ICD-9-CM codes, prescriptions for medication, and the patient's status in disease registries. Immunosuppression was a composite variable defined by the presence of any one of the following: cancer, use of immunosuppressive medications, chronic liver disease, or chronic renal disease. Smoking status was defined on the basis of data routinely collected during outpatient visits.[18] A detailed description of the classification of covariates is available as Supplementary Appendix 1 with the full text of this article at http://www.nejm.org.

Vaccinations

The Group Health Cooperative immunization data base, established in 1991, was used to identify pneumococcal and influenza vaccinations. To identify pneumococcal vaccinations recorded in the paper medical record but not in the immunization data base, such as those administered before 1991, the medical record was reviewed for all cohort members who did not have a record of pneumococcal vaccination in the data base.

Outcomes

The primary outcomes were hospitalization for community-acquired pneumonia, pneumonia in patients who were not hospitalized (outpatient pneumonia), and pneumococcal bacteremia. Hospitalizations for pneumonia and hospitalizations for pneumococcal bacteremia were presumptively identified on the basis of ICD-9-CM discharge codes (480 through 487.0 for pneumonia and 038.0, 038.2, 041.0, 041.2, and 320.1 for bacteremia). Cases of pneumococcal bacteremia were also identified from Group Health Cooperative laboratory data. Both outcomes were validated by review of the paper medical record with the use of a standardized data-collection instrument. A hospitalization was considered to be due to community-acquired pneumonia if, at the conclusion of the clinical evaluation, the treating physician considered pneumonia to be the cause of the presenting illness. The two sets of chart reviews — one for validation of outcome events and the other for vaccination status — were conducted at different times.

Outpatient pneumonia was defined as an outpatient or emergency room visit with an ICD-9-CM code for pneumonia (480 to 487.0) that was associated with both a prescription for an antibiotic and chest radiography within 14 days before or after the visit.

So as to permit comparison with other published studies, hospitalization with a discharge diagnosis code for pneumonia (regardless of the chart-validation status of the events) and death from any cause were evaluated as secondary outcomes.

STATISTICAL ANALYSIS

Crude event rates were calculated by dividing the number of cases by the person-time for each outcome, with person-time censored after the occurrence of a first event. Multivariate Cox proportional-hazards models with time-varying covariates[19] were used to evaluate the association between the receipt of pneumococcal vaccine and the time to a first outcome event during the study period. Pneumococcal-vaccination status was a time-varying covariate, and persons were considered to be vaccinated beginning 14 days after administration of the vaccine.

The models were adjusted for age at study entry; sex; nursing-home residence or nonresidence; receipt or nonreceipt of influenza vaccine; smoking status (currently smoking, not currently smoking, or no data); presence or absence of diabetes mellitus, coronary artery disease, immunosuppression, chronic lung disease, dementia or stroke, and hospitalization for pneumonia in the year before study entry; and number of outpatient visits in the year before study entry. Because the proportion of subjects with data on smoking status varied significantly according to pneumococcal-vaccination status at study entry, alternative analyses excluded subjects with no data on smoking status. Nursing-home residence or nonresidence and receipt or nonreceipt of influenza vaccine were time-varying covariates, whereas the other covariates were defined at study entry. Persons were classified as vaccinated with respect to influenza from 14 days after administration of the vaccine through the end of the corresponding influenza season, as defined on the basis of local and national surveillance data.[20-23]

RESULTS

CHARACTERISTICS OF THE STUDY SUBJECTS

The cohort consisted of 47,365 persons who were observed for a total of 127,180 person-years, of which 84,203 person-years (66 percent) followed pneumococcal vaccination. Of the 26,313 persons vaccinated before the beginning of the study (Table 1), 23,996 (91 percent) received pneumococcal vaccine most recently on or after their 65th birthdays, and 21,323 (81 percent) had been vaccinated within five years before the beginning of the study. Of the 21,052 persons who had not received pneumococcal vaccine before study entry, 10,869 (52 percent) were vaccinated during the study period.

OUTCOME EVENTS

A total of 2833 hospitalizations (of 2436 patients) were assigned an ICD-9-CM code for pneumonia (codes 480 through 487.0), and information on 2636 of these hospitalizations (93 percent) was available for review. Forty-eight of these were readmissions of patients with pneumonia, and 133 were associated with nosocomially acquired pneumonia. Of the remaining 2455 hospitalizations, a clinical diagnosis of community-acquired pneumonia was confirmed for 1600 (65 percent), which were accounted for by 1421 patients. An additional seven persons had an episode of community-acquired pneumonia, identified by chart review, during a hospitalization associated with an ICD-9-CM code for bacteremia. Thus, 1428 persons had a first hospitalization with confirmed community-acquired pneumonia during the study period. Sixty-one had pneumococcal bacteremia. During the study period, 3061 persons had

Table 1. Base-Line Characteristics of 47,365 Cohort Members According to Their Pneumococcal-Vaccination Status before Study Entry.

Characteristic	Unvaccinated before Entry (N=21,052)	Vaccinated before Entry (N=26,313)	P Value*
	no. of persons (%)		
Age group†			<0.001
65–74 yr	10,810 (51.3)	13,832 (52.6)	
75–84 yr	7,739 (36.8)	10,088 (38.3)	
≥85 yr	2,503 (11.9)	2,393 (9.1)	
Male sex	8,747 (41.5)	11,007 (41.8)	0.54
Duration of enrollment in Group Health Cooperative before study‡			<0.001
1–4 yr	4,109 (19.5)	2,935 (11.2)	
5–9 yr	1,877 (8.9)	2,156 (8.2)	
≥10 yr	15,066 (71.6)	21,222 (80.7)	
Nursing-home resident	621 (2.9)	507 (1.9)	<0.001
Smoking status			<0.001
Currently smoking	2,072 (9.8)	2,321 (8.8)	
Not currently smoking	15,098 (71.7)	21,531 (81.8)	
No data	3,882 (18.4)	2,461 (9.4)	
Coronary artery disease	3,843 (18.3)	5,911 (22.5)	<0.001
Immunocompromised	4,012 (19.1)	5,351 (20.3)	<0.001
Diabetes mellitus	2,394 (11.4)	4,654 (17.7)	<0.001
Chronic lung disease	1,702 (8.1)	2,839 (10.8)	<0.001
Dementia or stroke	1,150 (5.5)	1,385 (5.3)	0.34
No. of outpatient visits during previous 12 mo			<0.001
0	2,069 (9.8)	729 (2.8)	
1–10	11,275 (53.6)	13,560 (51.5)	
≥11	7,708 (36.6)	12,024 (45.7)	
Hospitalization for pneumonia in previous 12 mo§	219 (1.0)	319 (1.2)	0.079

* P values were calculated with the chi-square test.
† The median ages of the unvaccinated and vaccinated subjects were 74.7 and 74.5 years, respectively.
‡ The median duration of enrollment in the Group Health Cooperative for unvaccinated and vaccinated subjects was 17.1 and 19.1 years, respectively.
§ Pneumonia was defined by hospital-discharge codes 480 through 487.0 of the *International Classification of Diseases, 9th Revision, Clinical Modification*.[17]

at least one episode of outpatient pneumonia, and there were 5690 deaths from all causes.

PNEUMOCOCCAL VACCINATION AND OUTCOME EVENTS

In multivariate analyses of data on all subjects, receipt of pneumococcal vaccine was associated with a 44 percent reduction in the risk of pneumococcal bacteremia (Table 2). There was no significant association between vaccination and the risk of outpatient pneumonia or death, but vaccination was associated with a significantly higher risk of hospitalization with community-acquired pneumonia. In the analysis excluding the 13 percent of subjects with no data on smoking, this association was no longer statistically significant. There was no significant association between vaccination and all cases of community-acquired pneumonia, defined as a composite variable including both hospitalization for community-acquired pneumonia and outpatient pneumonia (hazard ratio, 1.07; 95 percent confidence interval, 0.99 to 1.14).

The relation of pneumococcal vaccination to the risk of outcome events did not vary according to the time since vaccination. For example, there was no consistent variation in the risk of hospitalization with community-acquired pneumonia that was associated with vaccination within an interval of 0 to 11 months (hazard ratio, 1.08; 95 percent confidence interval, 0.87 to 1.33), 12 to 23 months (hazard ratio, 1.23; 95 percent confidence interval, 1.02 to 1.49), 24 to 35 months (hazard ratio, 0.97; 95 percent confidence interval, 0.79 to 1.19), and 36 or more months (hazard ratio, 1.18; 95 percent confidence interval, 1.04 to 1.34), as compared with the reference group of persons who were not vaccinated.

In multivariate analyses, influenza vaccination was associated with a significant reduction in the risk of hospitalization with community-acquired pneumonia (hazard ratio, 0.78; 95 percent confidence interval, 0.65 to 0.95) and the risk of death (hazard ratio, 0.68; 95 percent confidence interval, 0.62 to 0.76) during influenza seasons, but it was not associated with the occurrence of outpatient pneumonia (hazard ratio, 1.12; 95 percent confidence interval, 0.97 to 1.30) or pneumococcal bacteremia (hazard ratio, 0.92; 95 percent confidence interval, 0.38 to 2.25) during influenza seasons.

In analyses restricted to immunocompetent persons who received influenza vaccine for each influenza season during which they remained in the cohort, pneumococcal vaccination was not associated with a reduction in the risk of hospitalization with pneumonia or of outpatient pneumonia. This result suggests that there is no added benefit of pneumococcal vaccination against those outcomes; however, pneumococcal vaccination was associated with a significant reduction in the risk of death (Table 3). Among immunocompetent persons with

Table 2. Incidence and Risk of Pneumonia, Pneumococcal Bacteremia, and Death from Any Cause in Relation to Pneumococcal-Vaccination Status.*

Variable	Hospitalization for Community-Acquired Pneumonia Verified by Medical-Record Review	Outpatient Pneumonia	Pneumococcal Bacteremia	Hospitalization with a Discharge-Diagnosis Code for Pneumonia†	Death from Any Cause
Unadjusted rate per 1000 person-years					
Unvaccinated	10.4	23.2	0.68	18.8	50.1
Vaccinated	11.8	25.7	0.38	19.9	42.0
Age-adjusted hazard ratio for all subjects (95% CI)	1.21 (1.08–1.35)	1.14 (1.06–1.23)	0.58 (0.35–0.96)	1.12 (1.02–1.22)	0.88 (0.84–0.93)
P value	0.001	≤0.001	0.03	0.01	<0.001
Multivariate-adjusted hazard ratio for all subjects (95% CI)	1.14 (1.02–1.28)	1.04 (0.96–1.13)	0.56 (0.33–0.93)	1.06 (0.98–1.16)	0.96 (0.91–1.02)
P value	0.02	0.31	0.03	0.16	0.19
Multivariate-adjusted hazard ratio for subjects with smoking-status data (95% CI)‡	1.11 (0.98–1.26)	1.02 (0.94–1.10)	0.53 (0.31–0.93)	1.05 (0.95–1.15)	0.94 (0.87–1.01)
P value	0.09	0.69	0.03	0.34	0.08

* The hazard ratios are for vaccinated subjects as compared with unvaccinated subjects. The multivariate hazard ratios were adjusted for age (65 to 74, 75 to 84, or more than 84 years); sex; nursing-home residence or nonresidence; receipt or nonreceipt of influenza vaccine; smoking status (currently smoking, not currently smoking, or no data); presence or absence of coronary artery disease, immunocompromised status, diabetes mellitus, chronic lung disease, and dementia or stroke; number of outpatient visits in the year before cohort entry (fewer than 6, 6 to 12, or more than 12); and any hospitalization for pneumonia in the year before study entry. CI denotes confidence interval.
† *International Classification of Diseases, 9th Revision, Clinical Modification* codes 480 through 487.0 denoted pneumonia.[17]
‡ The analysis excludes 6343 subjects for whom no data on smoking were available.

chronic lung disease, the condition most strongly associated with an increased risk of pneumonia in the multivariate models, there was no association between pneumococcal vaccination and the risk of pneumonia outcomes or death, but there was a reduction in the risk of pneumococcal bacteremia of borderline statistical significance.

DISCUSSION

In this retrospective study of a large cohort of 47,365 older adults, we did not identify an association between pneumococcal vaccination and a reduced risk of community-acquired pneumonia from any cause. On the assumption that *S. pneumoniae* was a common cause of pneumonia in this population, we infer from these results that vaccination was not highly protective against pneumococcal pneumonia without bacteremia. The association between vaccination and the specific outcome of pneumococcal pneumonia without bacteremia could not be directly assessed, because an etiologic agent is not identified for most cases of pneumonia. Our results are consistent with those of four meta-analyses of prospective randomized trials of pneumococcal polysaccharide vaccines, all of which concluded that there is no evidence that the vaccine is associated with a reduction in the risk of pneumonia from any cause among older adults.[24-27]

The analysis of our most specific outcome — pneumococcal bacteremia — indicated a reduction in risk that is consistent with the results of other studies. Our point estimate of vaccine effectiveness of 44 percent (95 percent confidence interval, 7 to 67 percent) is similar to the 47 percent estimate (95 percent confidence interval, 30 to 59 percent) in a case–control study of a group of mainly elderly subjects.[28] Since pneumococcal polysaccharide vaccine is recommended for all persons 65 years of age or older on the basis of evidence of its effectiveness against pneumococcal bacteremia[29] and since it is cost effective for this indication,[30] our results support the continued use of the vaccine in older adults for the prevention of invasive pneumococcal disease.

The size of our study, in terms of the total years of follow-up time and the number of pneumonia events observed, is a strength. The rate of hospitalization with community-acquired pneumonia that we observed, approximately 11 hospitalizations per

Table 3. Risk of Pneumonia, Pneumococcal Bacteremia, and Death from Any Cause According to Pneumococcal-Vaccination Status among Groups Defined by Immunocompetency, Presence of Chronic Lung Disease, and Receipt of Influenza Vaccine.*

Outcome	Immunocompetent (N=38,207)	Immunocompromised (N=9158)	Immunocompetent with Chronic Lung Disease (N=3126)	Immunocompetent with Receipt of Influenza Vaccine Annually (N=20,806)
Hospitalization for community-acquired pneumonia verified by medical-record review				
No. of events	959	469	257	479
Multivariate-adjusted hazard ratio (95% CI)	1.14 (0.99–1.31)	1.14 (0.94–1.39)	1.04 (0.79–1.36)	1.05 (0.86–1.29)
P value for adjusted hazard ratio	0.07	0.19	0.79	0.65
Outpatient pneumonia				
No. of events	2310	751	407	1315
Multivariate-adjusted hazard ratio (95% CI)	1.02 (0.93–1.11)	1.18 (0.95–1.31)	1.01 (0.81–1.25)	0.94 (0.83–1.06)
P value for adjusted hazard ratio	0.73	0.17	0.95	0.34
Pneumococcal bacteremia				
No. of events	39	22	6	19
Multivariate-adjusted hazard ratio (95% CI)	0.46 (0.24–0.87)	0.78 (0.32–1.87)	0.19 (0.04–1.09)†	0.35 (0.14–0.87)
P value for adjusted hazard ratio	0.02	0.57	0.06	0.02
Hospitalization with a discharge diagnosis of pneumonia (ICD-9-CM codes 480 through 487.0)				
No. of events	1628	808	383	815
Multivariate-adjusted hazard ratio (95% CI)	1.05 (0.94–1.17)	1.09 (0.93–1.26)	1.11 (0.88–1.37)	0.93 (0.80–1.09)
P value for adjusted hazard ratio	0.39	0.29	0.39	0.37
Death from any cause				
No. of events	3613	2077	482	1875
Multivariate-adjusted hazard ratio (95% CI)	0.88 (0.83–0.95)	1.09 (0.99–1.19)	1.00 (0.82–1.22)	0.85 (0.77–0.93)
P value for adjusted hazard ratio	0.005	0.08	0.96	<0.001

* The hazard ratios are for vaccinated subjects as compared with unvaccinated subjects and were adjusted, where appropriate, for age (65 to 74, 75 to 84, or more than 84 years); sex; nursing-home residence or nonresidence; receipt or nonreceipt of influenza vaccine; smoking status (currently smoking, not currently smoking, or no data); presence or absence of coronary artery disease, diabetes mellitus, chronic lung disease, and dementia or stroke; number of outpatient visits in the year before study entry (fewer than 6, 6 to 12, or more than 12); and any hospitalization for pneumonia in the year before cohort entry. CI denotes confidence interval, and ICD-9-CM the *International Classification of Diseases, 9th Revision, Clinical Modification*.[17]

† The hazard ratio was not adjusted for receipt or nonreceipt of influenza vaccine, sex, smoking status, presence or absence of dementia or stroke, and number of outpatient visits in the year before study entry because there were too few events to allow these variables to be estimated in the model.

1000 person-years, is similar to the rate of 10 per 1000 person-years reported for persons 65 years of age or older in an active surveillance study in Ohio.[1] The rate of pneumococcal bacteremia among unvaccinated cohort members in this study, 68 per 100,000 person-years, is similar to the overall rate of 58 per 100,000 person-years for persons 65 years of age or older reported by the Active Bacterial Core Surveillance system of the Centers for Disease Control and Prevention.[31] These similar event rates support the validity of our case-finding and outcome-validation methods.

On the basis of the event rates, our study had a power of 76 percent to detect a 15 percent reduction in the risk of hospitalization because of community-acquired pneumonia and a power of 98 percent to detect a 15 percent reduction in the risk of outpatient pneumonia associated with vaccination. On the assumption that 30 percent of cases of pneumonia from any cause are due to *S. pneumoniae*,[6] a 50 percent reduction in the risk of pneumococcal pneumonia would result in a 15 percent reduction in the risk of pneumonia from any cause. On the basis of this assumption, these estimates reflect the power of the study to detect at least a 50 percent decrease in the risk of pneumonia due to *S. pneumoniae* associated with vaccination. Our failure to detect such a decrease in risk does not exclude the possibility that the vaccine had some effect against pneumococcal pneumonia without bacteremia. Rather, it implies that, at a population level, the use of the pneumococcal polysaccharide vaccine

is unlikely to have a meaningful effect on the occurrence of community-acquired pneumonia among persons 65 years of age or older.

Our findings contrast with those of another retrospective study, which involved 1898 patients with chronic lung disease who were enrolled in an HMO in Minneapolis.[7] In that study, receipt of pneumococcal vaccine, as defined by administrative data, was associated with significant reductions in the risk of hospitalization for pneumonia and influenza, as defined by ICD-9-CM codes 480 through 487 (risk ratio, 0.57; 95 percent confidence interval, 0.38 to 0.84). Our results are not consistent with these findings, even when the data are analyzed for the subgroup of 3126 immunocompetent persons with chronic lung disease, as defined by our criteria (Table 3). The reasons for the disparate findings may include differences in the patterns of vaccine use, the methods of ascertainment of vaccination status, or the prevalence of pneumococcal pneumonia in the two study populations.

Ours is an observational study and is subject to the limitations of a nonrandomized study design. We obtained information on smoking status, nursing-home residence or nonresidence, and the presence or absence of chronic medical conditions from administrative data bases in an attempt to control for factors that could influence the relation between vaccination and the risk of outcome events. Ascertainment of medical conditions from administrative data is subject to some degree of misclassification,[32,33] and these methods do not allow patients to be classified according to the severity of their illness. Although we did control for the number of outpatient visits in the year before study entry as a proxy marker of the severity of illness, it is possible that residual confounding influenced our estimates of the association between vaccination and the risk of disease.

We found that pneumococcal vaccination was associated with a significant increase in the risk of hospitalization with community-acquired pneumonia, as verified by review of medical records, in the analysis of all subjects and a nonsignificant increase in this risk in some subgroup analyses. Of relevance to these findings are the results of a randomized, placebo-controlled trial of 23-valent pneumococcal polysaccharide vaccine in adults infected with the human immunodeficiency virus (HIV) in Uganda. In that trial, there was a significantly increased risk of invasive pneumococcal disease caused by vaccine serotypes within six months after vaccination among persons who had received the vaccine, as well as an increased risk of the overlapping outcome of pneumonia from any cause during that period (approximately a third of cases of pneumonia from any cause were associated with pneumococcal bacteremia).[34] The reasons for the increased risks associated with vaccination in the study in Uganda are not well defined, and an increased risk of disease has not been found in two observational studies of pneumococcal polysaccharide vaccine among HIV-infected persons in the United States.[35,36]

We found a reduced risk of pneumococcal bacteremia, the outcome most directly linked to pneumococcal infection, among vaccinated persons and no relation between the risk of hospitalization because of community-acquired pneumonia and the time since vaccination. We found no association between vaccination and the risk of outpatient pneumonia. Although these factors suggest a nonbiologic basis for the observed association between vaccination and the increased risk of hospitalization because of community-acquired pneumonia in our study, such as chance variation or the influence of residual confounding, the possibility of a true vaccine effect cannot be completely excluded.

Our results support the use of pneumococcal polysaccharide vaccine to prevent bacteremic disease in adults aged 65 years or over. The lack of evidence of effectiveness against pneumonia without bacteremia, however, underscores the critical need to evaluate other vaccine formulations for the prevention of noninvasive pneumococcal infections in adults. Two such possibilities are protein conjugate pneumococcal vaccines, such as the licensed 7-valent formulation recommended for use in young children, which may be effective against nonbacteremic pneumococcal pneumonia,[14] and protein vaccines, such as pneumococcal surface protein A formulations,[37,38] which may also offer the advantage of greater mucosal immunity than is conferred by polysaccharide vaccines.

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APPENDIX

The following persons are Vaccine Safety Datalink investigators: D.K. Shay, W.W. Thompson, J. Baggs, and R.T. Chen (National Immunization Program, Centers for Disease Control and Prevention, Atlanta); L.A. Jackson, K. Bohlke, and W.E. Barlow (Center for Health Studies, Group Health Cooperative, Seattle); S.B. Black, H.R. Shinefield, and R.L. Davis (Kaiser Vaccine Study Center, San Francisco); J.P. Mullooly (Center for Health Research, Northwest Kaiser Permanente, Portland, Oreg.); R. Platt and T.A. Lieu (Harvard Pilgrim Health Care, Boston); J.I. Ward, K.M. Zangwill, and S.M. Marcy (Center for Vaccine Research, Harbor–UCLA Medical Center, Torrance, Calif.); E.K. France (Clinical Research Unit, Kaiser Permanente of Colorado, Denver); and M. Goodman and E.A. Belongia (Health Partners Research Foundation, Minneapolis, and Marshfield Clinic, Marshfield, Wis.).

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