Impact of Pneumococcal Vaccination on Pneumonia Rates in Patients with COPD and Asthma

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BACKGROUND: Patients with chronic obstructive pulmonary disease (COPD) are included in several national pneumococcal vaccination recommendations whereas asthma patients are not. The objective of this study was to evaluate pneumonia-related hospitalization risk in patients with COPD or asthma and vaccination impact.

METHODS: We identified patients with documented pneumococcal vaccination from a cohort of veterans with either a diagnosis of asthma or COPD and their matched controls. Patients were identified between October 1, 1997 and September 30, 1998 and followed for 5 years. For each group we identified pneumococcal pneumonia hospitalizations and all pneumonia-related hospitalizations in the periods before and after vaccination. We estimated hospitalization rates and compared rates in the asthma and COPD groups to controls using negative binomial regression models.

RESULTS: We identified 16,074 COPD patients (average age 65.8 years), 14,028 controls for the COPD patients (average age 67.5 years), 2,746 asthma patients (average age 53.0 years), and 1,345 controls for the asthma patients (average age 59.2 years). Compared to controls, the adjusted risk of pneumococcal pneumonia hospitalizations before pneumococcal vaccination was COPD=8.02 (95% CI, 4.44–14.48) and asthma=0.76 (0.17–3.53). For any pneumonia-related hospitalization, the adjusted risk was COPD=3.91 (3.40–4.50) and asthma=1.45 (0.85–2.46). After vaccination, events decreased in all groups. The adjusted risk for pneumococcal pneumonia hospitalizations postvaccination was COPD=3.87 (2.55–5.88) and asthma=0.30 (0.04–1.99). For any pneumonia-related hospitalization the adjusted risk was COPD=3.71 (3.33–4.13) and asthma=0.79 (0.50–1.25).

CONCLUSIONS: This study supports the value of vaccinating COPD patients; however, the value of vaccination for asthma patients is less certain.

INTRODUCTION

The availability of pneumococcal vaccines makes pneumococcal infections a common vaccine-preventable infection.[1] The Centers for Disease Control and Prevention (CDC) have recommended pneumococcal vaccination in the elderly and others at high risk for serious pneumococcal infections and their complications.[2] Evidence for these recommendations ranges from high quality evidence of effectiveness to no evidence of effectiveness. Despite the recommendations, pneumococcal vaccination rates have historically been low for high-risk individuals.[3,4]

Patients with chronic obstructive pulmonary disease (COPD) are considered high risk. However, persons with asthma are not considered high-risk. Currently, there is a lack of evidence of the burden of pneumococcal disease and the effectiveness of the vaccination in patients with asthma. A Cochrane review highlighted the lack of evidence of the efficacy of pneumococcal vaccinations in asthma.[5]

Talbot et al.[6] recently reported that patients with asthma are at increased risk for pneumococcal disease. They found patients with asthma had a 2.4-fold increase in pneumococcal disease compared to those without asthma. Because asthma prevalence continues to increase, it is important to determine if patients with asthma should be included in pneumococcal vaccination recommendations.[7] Inclusion of these patients in the pneumococcal vaccination guidelines has the potential to prevent a number of pneumococcal infections and attenuate the burden of the disease, if asthma patients are at high risk. However, the benefit would not outweigh costs of vaccination if asthma patients are not at increased risk. Therefore, the objective of this study is to determine the risk of pneumococcal pneumonia and the impact of vaccination in adults with asthma compared to a high-risk group (persons with COPD) and the general population receiving care in the Veterans Health Administration (VHA).

METHODS

We conducted a retrospective cohort study using national VHA inpatient, outpatient, and mortality databases. We identified patients with COPD or asthma and control patients for these two groups, all of whom had documentation of pneumococcal vaccination during the observation period. To understand the potential impact of vaccination, we compared rates of pneumonia between patients with COPD or asthma and their controls during two separate periods. Comparisons were made

in the prevaccination period (time period before receiving pneumococcal vaccination) and the postvaccination period (time period after receipt of pneumococcal vaccination) to determine if risk was different between COPD and asthma patients and controls during the two periods. We focused on inpatient pneumonia diagnoses as events, as these are likely to have a higher degree of accuracy for pneumococcal-specific pneumonias than diagnoses in the outpatient setting, and we would expect pneumococcal vaccinations to effect pneumococcal pneumonia. Because not all pneumonias may be diagnosed based on culture results, we compared three categories of pneumonia: (1) pneumococcal, (2) pneumococcal or unspecified pneumonia, and (3) any pneumonia.

Cohort Identification

Four groups were identified: (1) COPD patients, (2) controls for COPD patients, (3) asthma patients, and (4) controls for asthma patients. Patients were eligible for inclusion if they were receiving VHA care between October 1, 1997 and September 30, 1998 (FY1998). To be included, patients had to have at least one visit in FY1997 to ensure they were receiving VHA health care services before the identification year. Patients were excluded if they died within the first 6 months of FY1998. In this analysis, only patients with documentation of receiving a pneumococcal vaccination during follow-up were included (Fig. 1).
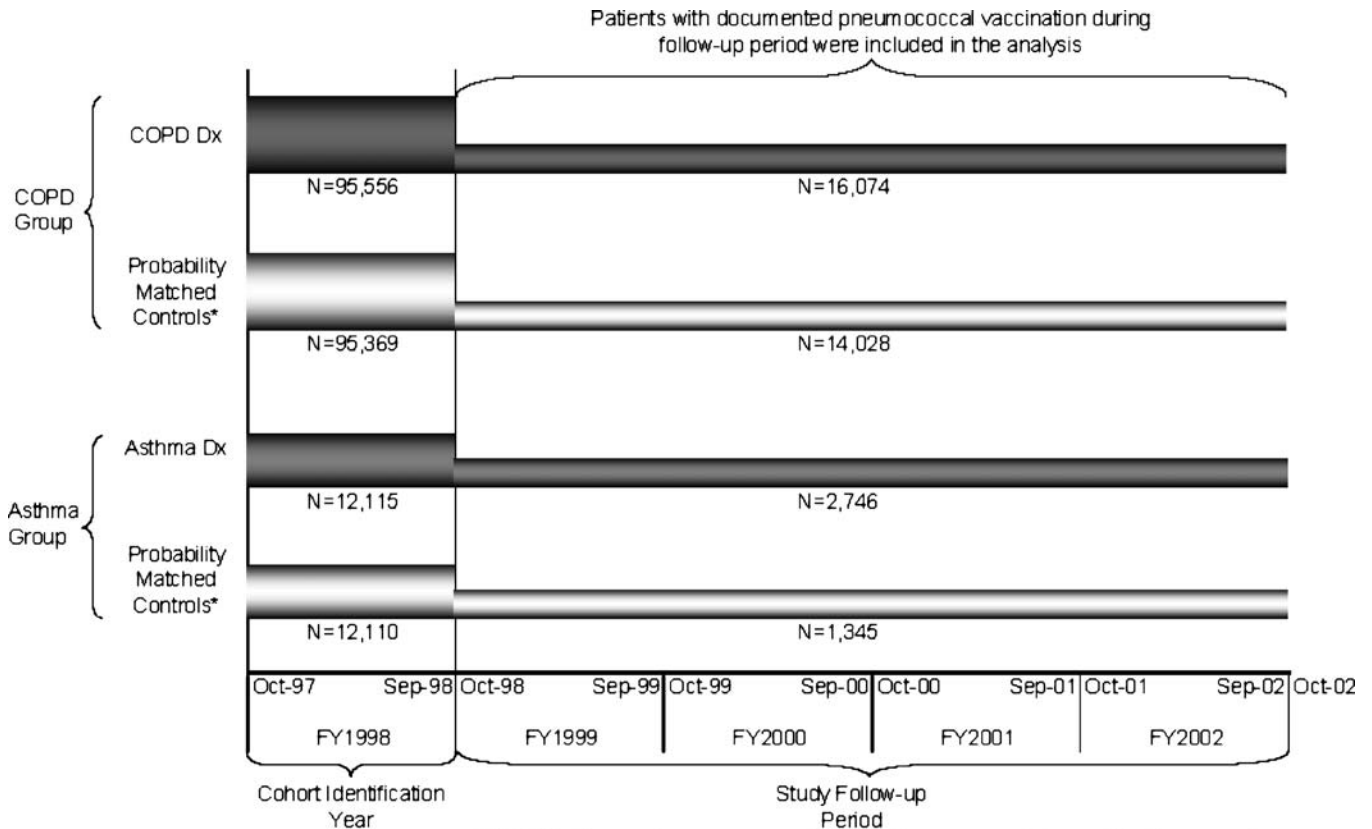
COPD and Asthma Cohorts

Inclusion in the COPD or asthma cohorts was based on presence of diagnostic codes in FY1998. Patients were required to have two outpatient visits or one hospitalization with an ICD-9 code for asthma or COPD. Patients were assigned to either asthma only or COPD only based on the diagnosis codes in FY1998 and excluded from the analysis if they had codes for both. Patients were also excluded if diagnosis codes in FY1997 did not match group assignment in FY1998.

Controls

We created a probability-matched sample of controls for the COPD and asthma patients. Control groups were matched to disease groups on age, sex, and region of the country. Patients were excluded from being controls if they had any diagnosis of asthma or COPD in FY1997 or FY1998.

Follow-up Period

The disease and control populations were followed over the same calendar time, which will account for secular trends related to infection control practices, treatment, or pneumonia risk that occurred over that period. The index visit was the date of the first visit for asthma or COPD or the first visit in FY1998 for the control patients. Patients were followed

Figure 1. Cohort identification process for patients included in the analysis.

from their index visit until death or end of the follow-up period (September 30, 2002). Person-time for each individual was calculated in the prevaccination and postvaccination period. The prevaccination person-time was the period from index date to vaccination date. The postvaccination person-time was the period from vaccination date until death or the end of follow-up. For each pneumonia event a person experienced during follow-up, 30 days were removed from the individual's person-time to avoid immortal time bias because they were not at risk for another pneumonia event during this time period based on how events were defined (see below).

Pneumococcal Vaccination

Pneumococcal vaccinations were identified by procedure codes (CPT or ICD-9 procedure code) during follow-up. The date the code first appeared was defined as the vaccination date.

Event Identification

Cases of pneumonia were identified using inpatient diagnoses. Pneumonias were categorized into three groups: (1) pneumococcal (ICD-9 481), (2) pneumococcal or unspecified pneumonia (ICD-9 481, 485, and 486), and (3) any pneumonia (ICD-9 481–486). For each pneumonia event identified, the date of the first appearing diagnostic code was the event index date. To avoid double-counting cases when follow-up care was being provided, we excluded events appearing within 30 days after the event index date. These were considered an extension of the initial event.

Analysis

For each patient, we used data from their index visit to describe baseline characteristics (age, sex, race, and region). To assess comorbidities and baseline health care utilization, we used the

Table 1. Baseline Characteristics of Patients Included in the Analysis

	COPD		Controls		P value	Asthma		Controls		P value
N	16,074		14,028			2,746		1,345		
Year of vaccination, *N* (%)					<0.001					0.274
1998	5,367	(33.4)	4,020	(28.7)		742	(27.0)	337	(25.1)	
1999	3,120	(19.4)	2,684	(19.1)		503	(18.3)	274	(20.4)	
2000	2,694	(16.8)	2,461	(17.5)		479	(17.4)	254	(18.9)	
2001	2,820	(17.5)	2,774	(19.8)		572	(20.8)	263	(19.6)	
2002	2,073	(12.9)	2,089	(14.9)		450	(16.4)	217	(16.1)	
Sex, *N* (%)										
Male	15,714	(97.8)	13,859	(98.8)		2,423	(88.2)	1,289	(95.8)	
Age group, *N* (%)										
≤34	31	(0.2)	7	(0.1)		269	(9.8)	41	(3.1)	
35–44	349	(2.4)	118	(0.8)		575	(20.9)	151	(11.2)	
45–54	2,227	(13.9)	1,137	(8.1)		720	(26.2)	328	(24.4)	
55–64	3,774	(23.5)	3,256	(23.2)		474	(17.3)	282	(21.0)	
65–74	6,365	(69.6)	6,267	(44.7)		510	(18.6)	385	(28.6)	
≥75	3,328	(20.7)	3,243	(23.1)		198	(7.2)	158	(11.8)	
Age, avg. (SD)	65.8	(10.1)	67.5	(9.1)		53.0	(14.2)	59.2	(13.1)	
Race, *N* (%)					<.001					0.003
White	10,664	(66.3)	7,344	(52.4)		1,105	(40.2)	607	(45.1)	
Black	1,516	(9.4)	1,792	(12.8)		410	(14.9)	171	(12.7)	
Others	549	(3.5)	701	(4.9)		329	(12.1)	192	(14.3)	
Unknown	3,345	(20.8)	4,191	(29.9)		902	(32.9)	375	(27.9)	
Comorbidities, *N* (%)										
HTN	6,605	(41.1)	7,029	(50.1)	<0.001	805	(29.3)	582	(43.3)	<0.001
IHD	1,476	(9.2)	985	(7.0)	<0.001	101	(3.7)	95	(7.1)	<0.001
Arthritis	2,760	(17.2)	2,338	(16.7)	0.250	333	(12.1)	192	(14.3)	0.054
Diabetes	2,239	(13.9)	3,157	(22.5)	<0.001	247	(9.0)	282	(21.0)	<0.001
Psych	1,550	(9.6)	920	(6.6)	<0.001	288	(10.5)	150	(11.2)	0.519
SA	327	(2.0)	162	(1.2)	<0.001	101	(3.7)	56	(4.2)	0.447
Dep	431	(2.7)	256	(1.8)	<0.001	97	(3.5)	34	(2.5)	0.087
Cancer	3,223	(20.1)	2,399	(17.1)	<0.001	288	(10.5)	161	(12.0)	0.154
Alcohol	1,225	(7.6)	566	(4.0)	<0.001	153	(5.6)	92	(6.8)	0.108
HF	1,859	(11.6)	706	(5.0)	<0.001	48	(1.8)	50	(3.7)	<0.001
AIDS/HIV	42	(0.3)	46	(0.3)	0.285	10	(0.4)	24	(1.8)	<0.001
Disease-related utilization, avg. (SD)										
Hosp	0.32	(0.8)				0.005	(0.1)			
ED visits	0.28	(0.9)				0.007	(0.1)			
Outpt	2.85	(4.6)				0.050	(0.3)			
Overall health care utilization, avg. (SD)										
Hosp	0.45	(1.0)	0.20	(0.6)	<0.001	0.18	(0.6)	0.23	(0.9)	0.060
ED visits	0.92	(2.0)	0.42	(1.2)	<0.001	0.84	(1.8)	0.46	(1.2)	<0.001
Outpt	20.62	(22.7)	14.54	(18.3)	<0.001	18.33	(21.8)	15.56	(22.8)	<0.001

Comorbidities: HTN=hypertension, IHD=ischemic heart disease, Psych=psychoses, SA=substance abuse, Dep=depression, Alcohol=alcoholism, HF=heart failure.
Health care utilization: Hosp=hospitalizations, Outpt=outpatient contacts, ED=emergency department.

Table 2. Follow-up Time and Mortality Rate in COPD and Asthma Groups

	COPD				Asthma			
	COPD		Controls		Asthma		Controls	
Duration of follow-up (y), mean (SD)								
Prevaccination	1.86	(1.46)	1.99	(1.47)	2.12	(1.48)	2.10	(1.47)
Postvaccination	2.53	(1.47)	2.59	(1.47)	2.64	(1.47)	2.55	(1.46)
Mortality, *N* (%)								
Died	1,591	(11.3)	3,718	(23.1)	86	(6.4)	105	(3.8)

1-year period preceding the index visit. Health care utilization for each patient was defined as the annual number of hospitalizations, emergency department (ED) visits and outpatient visits. For the disease groups, we determined the annual rate of disease-related health care utilization. For each disease category, we compared baseline variables using χ^2 tests for categorical variables and *t* tests for continuous variables.

For disease groups and controls, we estimated pneumonia-related hospitalization rates in prevaccination and postvaccination periods. We used negative binomial models to compare adjusted relative risk between the disease group and controls in the prevaccination and postvaccination periods. Negative binomial models were used because the rates represent a nonnegative count function with overdispersion.[8–11] Models were adjusted for age, sex, comorbidities (each of 11 comorbidities included as a dichotomous variable), and baseline health care utilization.

RESULTS

The proportion of patients with pneumococcal vaccination during follow-up was 16.8% in the COPD group, 14.7% in the COPD controls, 22.7% in the asthma group, and 11.1% in the asthma control group. This resulted in 16,074 patients with COPD and 14,028 COPD controls that were included in the analysis (Fig. 1). There were 2,746 patients with asthma and 1,345 asthma controls included.

The characteristics of patients included are shown in Table 1. The largest percentage in each group was vaccinated in 1998; however, the percentage was between 15% and 20% in each subsequent year. In the asthma group, a higher percentage of the disease group vaccinated was females compared to controls (11.8% vs 4.2%). The average age of controls was higher than the disease group.

Compared to patients excluded from the analysis, the patients with vaccinations during follow-up were older in each of the groups with the exception of the COPD disease group. The patients in the analysis were similar to those excluded with respect to baseline ED visits and outpatient visits. The patients excluded (i.e., no vaccination during follow-up) had higher rates of hospitalization than those included.

Prevaccination and postvaccination follow-up times were similar between disease groups and controls (Table 2). Rates of pneumonia-related hospitalizations occurring during prevaccination and postvaccination periods are shown in Table 3. The rate of pneumococcal pneumonia-related hospitalizations decreased in COPD patients from 0.47 per 100 person-years in the prevaccination period to 0.37 per 100 person-years in the

postvaccination period. The COPD controls had a small increase in rates from 0.05 cases per 100 person-years prevaccination to 0.08 cases per 100 person-years postvaccination. The adjusted relative risk between the COPD patients and controls went from 8.02 (95% CI 4.44 to 14.48) in the prevaccination period to 3.87 (95% CI 2.55 to 5.88) in the postvaccination period.

The rates of pneumococcal or unspecified pneumonia hospitalizations increased in both the COPD and control group from prevaccination to postvaccination periods (Table 3). The adjusted relative risk for pneumococcal or unspecified pneumonia hospitalizations for COPD patients compared to controls was similar in the prevaccination and postvaccination periods (3.84 [95% CI 3.31 to 4.45] vs 3.61 [95% CI 3.22 to 4.05]).

For asthma patients and controls, the rate of pneumococcal pneumonia-related hospitalizations decreased from prevacci-

Table 3. Pneumonia-Related Hospitalization Rates During Follow-up by Disease Group in the Vaccinated Cohort (Rates Presented per 100 Person-Years)

	Crude rates per 100 person-y		Adjusted relative risk	95% CI
	Disease group	Controls		
COPD				
Pneumococcal pneumonia only				
Prevaccination	0.47	0.05	8.02	4.44 to 14.48
Postvaccination	0.37	0.08	3.87	2.55 to 5.88
Pneumococcal and unspecified pneumonias				
Prevaccination	4.83	0.91	3.84	3.31 to 4.45
Postvaccination	5.90	1.39	3.61	3.22 to 4.05
Any pneumonia				
Prevaccination	5.77	1.06	3.91	3.40 to 4.50
Postvaccination	7.07	1.62	3.71	3.33 to 4.13
Overall hospitalizations				
Prevaccination	64.71	52.00		
Postvaccination	45.64	23.72		
Asthma				
Pneumococcal pneumonia only				
Prevaccination	0.09	0.21	0.76	0.17 to 3.53
Postvaccination	0.03	0.09	0.30	0.04 to 1.99
Pneumococcal or unspecified pneumonia				
Prevaccination	1.11	0.70	1.78	0.97 to 3.26
Postvaccination	0.99	1.17	0.81	0.50 to 1.31
Any pneumonia				
Prevaccination	1.27	0.99	1.45	0.85 to 2.46
Postvaccination	1.11	1.34	0.79	0.50 to 1.25
Overall hospitalizations				
Prevaccination	49.59	52.79		
Postvaccination	17.75	22.17		

nation to postvaccination (Table 3). The rates were much lower than in COPD patients. Furthermore, there were no significant differences in the relative risk of pneumonia between asthma patients and controls in either the prevaccination period or postvaccination period.

DISCUSSION

The aim of this study was to evaluate the impact of pneumococcal vaccination on rates of pneumonia-related hospitalizations in patients with COPD and asthma relative to patients without those respiratory diseases. COPD patients with a vaccination had decreased rates of pneumococcal pneumonia hospitalizations after vaccination. However, they still had nearly a fourfold increase in the risk of pneumococcal pneumonia hospitalizations compared to control patients. The rates of pneumococcal pneumonia hospitalizations were also lower in asthma patients after vaccination. But unlike with COPD, the adjusted relative risk of pneumococcal pneumonia hospitalizations for asthma patients was not significantly different from controls.

Our findings support the observation that patients with COPD have a substantially elevated risk of pneumococcal pneumonia-related hospitalizations. Pneumococcal vaccination reduces the magnitude of the increased risk; however, risk remains elevated in COPD patients compared to similar patients without COPD. The results in the asthma analysis are different. Asthma patients did not have a higher risk of pneumococcal pneumonia than similar patients without asthma. The risk for pneumococcal pneumonia in asthma patients is not different from control patients, and the rate in asthma patients is much lower than in patients with COPD.

With respect to the rate of pneumonia in patients with asthma relative to controls, our findings are in contrast to results recently reported by Talbot et al.[6] They found persons with asthma had a 2.4-fold increased risk of invasive pneumococcal disease compared to controls. Before receiving a vaccination, we found the rate of pneumococcal pneumonia was lower in asthma patients than controls. For pneumococcal plus unspecified pneumonias the rate in the asthma group was 1.78 times higher than controls and for all pneumonias was 1.45 times higher than controls; however, neither was statistically significant. There are substantial differences between the two studies that could account for the differences. Talbot et al. focused on invasive pneumococcal disease while we focused solely on pneumonias as a potentially serious complication in those with chronic respiratory disease. In addition, Talbot et al. used identification of pneumococcal events in a focused surveillance program while we relied on administrative data. Finally, the ages of the asthma patients studied are different, the average age in the Talbot et al. analysis was 28.5 years and in our asthma population it was 53.0 years. Thus, it may not be surprising that differences exist in the results from the two studies.

The benefit of pneumococcal vaccination has been studied in both randomized trials and observational studies. There have been several meta-analyses that summarize the results of randomized trials.[12–16] The results of some of these meta-analyses find no benefit for pneumococcal vaccination in the elderly or other high-risk populations.[12,13,15,16] When observational studies in the elderly or those with chronic disease

were systematically reviewed, the use of pneumococcal vaccine was associated with a 32% reduction in the risk of all-cause pneumonia.[17] Observational studies provide evidence for the effectiveness of pneumococcal vaccination in high-risk populations. Unlike previous studies (other than those in HIV patients), our study focused on a specific subset of patients included in vaccination recommendations (COPD patients) and compared the findings in those patients with results from patients that may also be at an elevated risk for pneumococcal pneumonia and could potentially benefit from vaccination.

There are limitations that need to be acknowledged. First, this is an observational study that utilizes administrative data in identifying the cohort and the presence of pneumococcal vaccination and pneumonia-related hospitalizations. The interpretation of the results is impacted by the validity and accuracy of diagnoses in administrative data. The validity of COPD and asthma diagnoses has varied across administrative databases[18–21] and we have found that 80.8%, from a sample of 120 patients with a diagnosis of COPD in the VHA system, had lung function tests consistent with the diagnosis (unpublished data). To reduce diagnostic misclassification, we used a definition of two rather than one outpatient diagnosis or one inpatient diagnosis. Yet, some patients included in the disease groups may not have either COPD or asthma, but it is likely that they have symptoms and complaints consistent with the disease and would be considered clinically as having the disease. In this light, it is important to consider that the decision to recommend pneumococcal vaccination to a patient if they fall into a high-risk group will most likely be based on diagnoses reported in the patient's records, their self-reported diagnoses, or their symptoms and not the result of lung function tests to confirm the patient has either COPD or asthma. Therefore, these results provide a "real world" look at the effectiveness of pneumococcal vaccination in patients with diagnoses of COPD or asthma.

It is also important to consider the validity of pneumonia diagnoses. We were unable to confirm diagnoses through culture results and rely on the accuracy of the diagnosis in administrative data. However, because not all pneumonias may be diagnosed based on culture results we considered three separate end points. Previous observational studies have looked at all-cause pneumonias as the outcome rather than focusing on pneumococcal pneumonia specifically.[17] We felt examining pneumococcal pneumonias specifically was important because that is where we expect to see the most effect and by limiting the analysis to hospitalizations the likelihood of the diagnosis being based on culture results is higher than using outpatient diagnoses.

Because this is an observational study and patients were not randomized to receive pneumococcal vaccination, there may be selection bias involved in choosing patients for vaccination. That is, the vaccinated patients are likely to be different from the unvaccinated patients.[22] By focusing solely on patients vaccinated, we remove concerns about selection bias between vaccinated and nonvaccinated patients and are still able to compare the relative impact of pneumococcal pneumonia within disease groups and attempt to control for any remaining differences using regression models. We relied on the presence of vaccination codes in administrative databases to identify our vaccinated subgroups. It is possible for pneumococcal vaccines to be administered in several settings and documentation of vaccination in the medical record may

not occur. But we focus only on those with documented vaccination and Weaver et al.[23] have shown in a sample of VHA patients that more than 80% of those that had a code for vaccination in the administrative data reported receiving pneumococcal vaccination.

Another issue with reliance on administrative data to identify vaccinations is the date of vaccination. We used the first code for a vaccination that appeared during the follow-up to define the date of vaccination. It is possible that in some cases the date the code appeared in the administrative data is not reflective of the actual vaccination administration date. If this were true, patients would actually have been vaccinated in the prevaccination period. However, there would be no reason to believe that such misclassification of exposure date would be differential between disease and control groups. Even if differential misclassification existed, we would presumably be seeing lower rates of events in the prevaccination period than if all patients had not been vaccinated during this period. Therefore, our estimate of the benefit of vaccination would be a lower (conservative) estimate of the benefit of vaccinating patients in these groups.

One needs to be cautious when drawing conclusions about the benefit of an intervention when studied in a naturalistic setting and pre- and postcomparisons are made. There is concern that results may be an ecological fallacy because of several factors and cannot be attributed to pneumococcal vaccination. In this study, we are following a group of patients with chronic respiratory disease that is aging over the time period. We would expect increases in rates of pneumonias over the time period as the diseases progress and the cohort ages. However, our results show that rates of pneumococcal events decreased in each group after vaccination administration. It would be difficult not to conclude that vaccination had an impact and simply explain the results away as an ecological fallacy. Finally, because the subset of patients included in the analysis represents the minority of patients initially identified, it is unclear whether these findings would apply to the entire population with COPD or asthma.

In conclusion, our study showed that pneumococcal pneumonia produces substantial disease burden in patients with COPD. The use of pneumococcal vaccination can reduce that burden, but the rate of events still remains higher than in similar patients without COPD. In asthma patients, the rates of pneumococcal events were much lower than in COPD patients. But similar to COPD patients, the rate of pneumococcal hospitalizations decreased in patients that received a pneumococcal vaccination. Importantly, the rates were not different from similar patients without asthma. This study supports the value of vaccinating COPD patients and their inclusion in pneumococcal vaccination recommendations; however, the value of vaccination for asthma patients is less certain and it may not make sense to include them as a high-risk group simply based on an asthma diagnosis.

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