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Hospitalizations associated with pneumococcal infection within the Medicare population among vaccinated and non-vaccinated patients

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Hospitalizations Associated with Pneumococcal Infection within the Medicare Population among Vaccinated and Non-vaccinated Patients

by

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A thesis submitted in partial fulfillment
of the requirements for the degree of
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DEDICATION

"A little learning, indeed, may be a dangerous thing, but the want of learning is a calamity to any people." -Sir Frederick Douglass

This research is dedicated to my parents, Willie Lloyd and the late Patricia A. Webb, who taught me that education is everything and without it we are subject to settling for a lifetime of hand-me-downs. Knowing that I was capable of more they never allowed me to settle for barely getting by (ie, C's). My mother would say, "C's have no place in this house." Their tough love has made me the well balanced individual that I am today.

I also dedicate the completion of this degree and research to my godparents, Stephanie Hill and Wilson Etienne, as they have provided parental oversight, a piece of mind, financial support, and unconditional love for the past eight years (seems like a lifetime)! To my sister, brother, niece, and great aunt (Satin Webb, Jody Webb, Santina Walker, and Elaine Walker) thanks for understanding and supporting my decision to complete my Pharm.D. and 2-year fellowship along with my Master of Science in Public Health (M.S.P.H). Thanks for taking care of one another as best you could given the circumstances.

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"Gratitude is something of which none of us can give too much. For on the smiles, the thanks we give, our little gestures of appreciation, our neighbors build up their philosophy of life." -A.J. Cronin

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Hospitalizations Associated with Pneumococcal Infection within the Medicare Population Among Vaccinated and Non-vaccinated Patients

Silky F. Webb, Pharm.D.

ABSTRACT

Background: *Streptococcus pneumoniae* is the primary causative agent of pneumonia in older adults. Vaccination is the only tool to protect against pneumococcal infection; however, vaccination rates remain far below the Healthy People 2010 objective of 90% coverage. The number one reason for such low rates is attributed to controversy over the protective efficacy of the vaccine in preventing nonbacteremic pneumonia (eg, community-acquired pneumonia [CAP]).

Objectives: The primary objectives of this study were to assess the incidence of pneumonia, pneumonia requiring hospitalization, and pneumonia hospitalization costs.

Methods: In this retrospective cohort study of Medicare beneficiaries aged 65 years in 2003, subjects were selected based on exposure status. Exposure was defined as receipt of the 23-valent pneumococcal polysaccharide vaccine (PPV23). Vaccinated persons were then matched 1:1 on gender and the presence of any comorbidity to unvaccinated persons. Subjects were followed up for 1 year (January 1, 2004 through December 31, 2004). The primary outcomes were pneumonia, pneumonia requiring hospitalization, and hospitalization costs. Mantel-Haenszel chi-square or logit was used to estimate the relative risk (RR) associated with vaccination and each outcome and Proc Ttest was used to test the difference between mean hospital costs of the vaccinated and non-vaccinated.

Results: During the follow-up period, 443 patients were diagnosed with pneumonia; 266 had previously been vaccinated and 177 had no documented receipt of prior vaccination. Results of the Chi-square analysis revealed a significant association between vaccination and the risk of pneumonia, as the vaccinated were 50% more likely to develop pneumonia than were the non-vaccinated (Adjusted RR: 1.50; 95% CI: 1.25, 1.81). Approximately 67% of patients diagnosed with pneumonia required hospitalization; of which, 183 were previously vaccinated and 115 had

no documented receipt of prior vaccination. There was no association between vaccination and risk of pneumonia requiring hospitalization (*P* value 0.4001). However, the vaccine was associated with a significant reduction in hospital costs (*P* value 0.004).

Conclusions: The results of this study suggest that use of the vaccine may be associated with cost savings due to a reduction in hospitalization.

CHAPTER ONE

Introduction

Pneumococcal infection is a major source of morbidity and mortality in older adults over age 65 years (Loeb, 2003). The primary causative agent of pneumococcal infection is *Streptococcus pneumoniae* (CDC, 2006; Kupronis *et al*, 2003; Loeb, 2003). Upon colonizing the respiratory tract, *S. pneumoniae* can cause disseminated invasive infections, including bacteremia/septicemia and meningitis; pneumonia and other lower respiratory tract infections; and upper respiratory tract infections, including otitis media and sinusitis (DHHS, 1997). In adults, 60% to 80% of pneumococcal bacteremia is associated with pneumonia (DHHS, 1997). Adults older than 65 years are at a particularly higher risk for *S. pneumoniae* colonization due to their advanced age, frequent presence of chronic illnesses, and institutionalism (ie, residence within a long term care facility [LTCF]). In the United States (U.S.) and Canada, it is estimated that between 5,000 and 30,000 cases of pneumococcal infection per annum occur in elderly patients (Butler *et al*, 1999). Case-fatality rates in this population range from 30% to 40% (CDC, 2006; Kupronis *et al*, 2003).

Nonbacteremic pneumonia, the most common manifestation of pneumococcal infection among the elderly (Jackson *et* al, 2003), exerts a great burden on the individual and society (De Graeve *et al*, 2004). Hospitalization due to nonbacteremic community-acquired pneumonia (CAP) in the U.S. has been estimated to range from $7,000 to $8,000 per admission or $4 million per 100,000 population, accounting for approximately 90% of the total cost to treat nonbacteremic CAP (De Graeve *et al*, 2004).

There are currently two 23-valent pneumococcal polysaccharide vaccines in the U.S.; manufactured by Merck and Company, Inc. (Pneumovax® 23) and Lederle Laboratories (Pnu-Immune® 23). In late 1983, the reformulated 23-valent vaccine replaced the 14-valent vaccine. The 23 serotypes represented in the vaccine cause 85% of all invasive infections (DHHS, 1997). The pneumococcal vaccine is recommended for those individuals at high risk for infection; this

includes individuals older than 65 years, residents of LTCFs, and individuals with multiple comorbidities and chronic conditions (DHHS, 1997). Unlike the influenza vaccine which is recommended yearly, the pneumococcal vaccine has been recommended as a once in a lifetime injection. Revaccination is recommended for those persons aged 65 years who received their primary vaccination ≥5 years previously (DHHS, 1997).

One of the national Healthy People 2010 objectives is to achieve 90% pneumococcal vaccination coverage among residents of LTCFs and older adults greater than 65 years (DHHS, 2000). Based upon the latest estimates from the Centers for Disease Control and Prevention (CDC), vaccination rates remain far below this goal as only 49.9% of those aged 65 to 74 years and 60.9% of those 75 years and older report ever being vaccinated (CDC, 2001b). One reason for low immunization rates may be continued controversy over the clinical efficacy of the vaccine in this population (Butler *et* al, 1993).

Problem Statement

Previous studies on the cost-effective of the pneumococcal polysaccharide vaccine in people 65 years and older in the U.S. have been positive (Sisk et al, 1986; Sisk et al, 1997). The results of these studies are limited as the efficacy of the vaccine in the prevention of pneumonia is assumed to be equivalent to the efficacy of the vaccine in the prevention of invasive disease (Sisk et al, 1986). Despite this major flaw and controversy over the protective efficacy of the vaccine in the prevention of nonbacteremic pneumonia, the Advisory Committee on Immunization Practices (ACIP) has considered lowering the universal vaccination age from 65 years to 50 years (Sisk et al, 2003). Inconclusive results on the clinical efficacy of the vaccine in the prevention of nonbacteremia pneumonia warrant additional studies (Simberkoff et al, 1993).

Research Objectives and Hypotheses

In an attempt to understand why such low rates of pneumococcal immunization exist among the older adults, we must gain an understanding of the patient and provider factors that surround the administration of the vaccine. In addition, until we gain more consistent results, more studies are warranted on the efficacy of the vaccine against nonbacteremic pneumococcal

infections in individuals 65 years and older. The primary objectives of this study were to assess the incidence of pneumonia, incidence of pneumonia requiring hospitalization, and pneumonia hospitalization costs among vaccinated and non-vaccinated Medicare beneficiaries. As a secondary objective, we will describe the demographic characteristics of and circumstances surrounding the administration of the pneumococcal polysaccharide vaccine. Our research objective and major hypotheses are summarized in Table 1.

Table 1. Research Objectives: Questions and Hypotheses

Primary Research Objectives Questions & Null Hypotheses (Ho)
#1. To assess the incidence of pneumonia in vaccinated and non-vaccinated patients Ho: There is no difference in the incidence of pneumonia in those that are vaccinated versus those that are not vaccinated
#2. To assess the incidence of pneumonia requiring hospitalization in vaccinated and non-vaccinated patients Ho: There is no difference in hospitalization rates among patients that are vaccinated versus those that are not vaccinated
#3. To assess the hospitalization costs among the vaccinated and non-vaccinated Ho: There is no difference in hospitalization costs among patients that are vaccinated versus those that are not vaccinated

In the next section, we will highlight the findings of studies conducted among the elderly, those aged at least 55 years. Because the incidence of *S. pneumoniae* strains vary around the world, our review was restricted to studies conducted in the U.S. elderly population. Additionally, because the 14-valent vaccine was replaced by the 23-valent vaccine in late 1983, we also restricted the review to include only those studies evaluating the protective efficacy of the 23-valent vaccine.

Literature Review

A Pubmed search was conducted for 1983 to January 2007 using “pneumococcal”, “vaccine”, “randomized”, “efficacy”, “effectiveness”, “cohort studies”, “case-control studies”, “resource utilization” and combinations of these and other Boolean search terms. So that relevant studies on older adults would not be omitted, search restrictions did not include age. The bibliography of a meta-analysis (Dear *et al*, 2006) of previous pneumococcal vaccine trials

was also used to identify additional studies. Using the methods described, numerous studies were identified. Studies that did not include the 23-valent pneumococcal polysaccharide vaccine (PPV23) were excluded.

As a result, a total of eight observational studies were identified and are summarized in the Appendix. Of the studies identified, there was one indirect cohort study (Butler *et al*, 1993); two retrospective cohort studies (Jackson *et al*, 2003; Fisman *et al*, 2001); one nested case-control study (CDC, 2001c); three matched case-control studies (Sims *et al*, 1988; Shapiro *et al*, 1991; Farr *et al*, 1995); and one population-based case series (Chi *et al*, 2006). All but four observational studies exclusively addressed the protective efficacy of the vaccine in older adults aged 55 years or older (Fisman *et* al, 2006; Butler *et* al, 1993; Shapiro *et al*, 1991; Forrester *et al*, 1987). Despite enrolling children aged 2 years and greater, Shapiro *et* al (1991), and Butler *et al* (1993) estimated vaccine efficacy for subgroups that included immunocompetent patients aged 65 to 74 years and immunocompetent patients 65 years and older, respectively. In general, across all of the case-control studies cases, cases were identified as people with positive cultures (CDC, 2001c; Farr *et al*, 1995; Shapiro *et al*, 1991; Sims *et al*, 1988). The indirect cohort study conducted by Jackson *et al* (2003) drew from the population of a managed care organization (Group Health Cooperative; Washington State). Chi *et al* (2006) drew from the same study population to conduct a population-based case-series. The indirect cohort study conducted by Butler *et al* (1993) analyzed national surveillance data for pneumococcal infections submitted to the CDC by U.S. hospital laboratories. The 23-valent vaccine was used exclusively in four trials (Sims *et al*, 1988; Shapiro *et al*, 1991; Butler *et al*, 1993; Farr *et al*, 1995). In another four trials, patients were adminstered either the 14-valent vaccine (PPV14) or PPV23 (CDC, 2001c; Jackson *et al*, 2003; Fisman *et al*, 2006; Chi *et al*, 2006).

Shapiro *et al* (1991) conducted a hospital-based case-control study. From 1984 to 1990, patients from 11 hospitals with laboratory-confirmed pneumococcal infection and an indication for pneumococcal vaccine were enrolled as cases. Cases and controls were matched 1:1 on age, underlying illness, and site of hospitalization. The protective efficacy of the vaccine in the overall population was 56% (95% confidence interval [CI]: 42%, 67%). The vaccine was only 21% (95%

CI: -55%, 60%) effective in the immunocompromised patients; the protective efficacy in this subgroup was significantly less than that in the immunocompetent subgroup which included adults aged 55 years and older (1-OR: 61%; 95% CI: 47%, 72%). When stratified by increasing age, the protective efficacy of the vaccine was only statistically significant for those aged 55 to 74 years. Based on these data, the authors concluded that there may be some benefit in vaccinating the elderly, even at the extremes of ages (Shapiro *et al*, 1991).

Sims *et al* (1988) conducted a multicenter, case-control study of hospitalized older adults 55 years of age and older with pneumococcal bacteremia, meningitis, or any other bacteriologically confirmed pneumococcal infection during a 5-year period. Patients were excluded from the study if there was evidence of immunosuppression due to disease or iatrogenic disease. A total of 366 patients were included in the study; their mean age was 69.5 ± 9.5 years. After logistic regression modeling to control for confounding variables, the vaccine efficacy was calculated to be 70% (95% CI: 37%, 86%). The authors of this study concluded that the vaccine confers substantial protection from serious pneumococcal infections in immunocompetent elderly (Sims *et al*, 1988). Another case-control study conducted by Farr *et al* (1995) demonstrated an 81% (95% CI: 34%, 94%) protective efficacy. The mean age of cases and controls in this study were 52.8 ± 2.0 years and 57.7 ± 1.5 years, respectively. In an attempt to ensure that cases and controls were equally likely to have a prior exposure to pneumococcal vaccine, the logistic regression model matched on eight variables. To date no other case-controls has ever matched on this number of variables. The results of this study further support the conclusions drawn by previous studies (Farr *et al*, 1995).

In a nested case-control study conducted in 2001 among residents of a nursing home in New Jersey (USA), the risk factors for pneumococcal pneumonia were evaluated (CDC, 2001c). Cases included nine residents hospitalized with pneumonia. Controls were matched to cases in a 2:1 ratio and randomly selected from among nursing home residents without pneumonia symptoms residing in the same wing where most of the case-patients had resided from March 1, 2001 through April 26, 2001. Median age of the cases and controls was similar; 86 years and 85 years, respectively. Pneumonia was strongly associated with failure to be vaccinated as zero of 9

case-patients developed disease versus 9 of 18 controls (odds ratio [OR]: 0; 95% CI: 0.0, 0.7) (CDC, 2001c). This study further underscores the importance of pneumococcal vaccination in the elderly.

Jackson *et al* (2003) conducted a retrospective cohort study of elderly members of a staff-model managed care organization, Group Health Cooperative (GHC), over a 3-year period. The primary outcomes were hospitalization due to community-acquired pneumonia (validated by chart review), pneumonia treated in the outpatient setting (determined from administrative data sources), and pneumococcal bacteremia. Using multivariate Cox proportional-hazard models to control for age, sex, nursing-home residence or nonresidence, smoking status, medical conditions, and receipt or nonreceipt of influenza vaccine, the authors evaluated the association between pneumococcal vaccination and risk of each outcome. Receipt of the pneumococcal vaccine was associated with a significant reduction of pneumococcal bacteremia (hazard ratio [HR]: 0.56; 95% CI: 0.33, 0.93) but a slightly increased risk of hospitalization for pneumonia (HR: 1.14; 95% CI: 1.02, 1.28). On the other hand, receipt of pneumococcal vaccination did not alter the risk of outpatient pneumonia (HR: 1.04; 95% CI: 0.96, 1.13) or any cause of community-acquired pneumonia, whether or not it required hospitalization (HR: 1.07; 95% CI: 0.99, 1.14). In another retrospective cohort study conducted by Fisman *et* al (2006), hospitalized vaccine recipients with community-acquired pneumonia were less likely to die of any cause than were individuals with no record of vaccination (OR: 0.50; 95% CI: 0.43, 0.59). In comparison to nonvaccination, vaccination was also noted to lower 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 (*P* value <0.001) (Fisman *et al*, 2006). Based on the results of these studies, pneumococcal vaccine is effective in preventing bacteremic pneumonia; however other strategies are needed to prevent nonbacteremic pneumonia (Fisman *et* al, 2006; Jackson *et al*, 2003).

Investigators of the CDC conducted an indirect cohort study to test their hypothesis that pneumococcal infections occurring in vaccinated individuals should be fess frequently due to vaccine serotypes than infections occurring in unvaccinated controls (Butler *et al*, 1993). Patients aged 2 years or more who were of known vaccination status and vaccination date, who had onset

of illness between May 1978 and April 1992 but greater than 30 days from vaccination until onset of illness, and from whom a vial isolate from blood or cerebrospinal fluid (CSF) was received and serotyped were included in the study. For immunocompetent adults older than 65 years, the study demonstrated a vaccine efficacy of 70% (95% CI: 57%, 85%). The authors of this study concluded that pneumococcal polysaccharide vaccine effectively prevents invasive disease due to pneumococcal serotypes included in the vaccine in several patient populations for whom the vaccine is currently recommended. They also concluded that the vaccine may provide a shorter period of protection as well as less protective efficacy among patients immunocompromised by certain underlying illnesses, including older age (Butler *et al*, 1993).

Chi *et al* (2006) conducted a population-based case series of community-dwelling adults aged 65 years and older. Patients with at least 2 years of enrollment in GHC and a diagnosis of pneumococcal bacteremia (confirmed by a positive blood culture or chart review) between 1988 and 2002 were included in the study. A total of 200 elderly patients were identified; on average they had aged 78 years and 61% were female. Prior to the onset of bacteremia, 40% of patients had chart-documented receipt of pneumococcal vaccination. Approximately 10% of the study population was treated on an outpatient basis; of the remainder that was hospitalized (90%), 16% were admitted to an intensive care unit (ICU). Of the survivors, 43% were discharged to a higher level of care. After using a logistic regression model to control for age, sex, and pneumococcal vaccination status, predictors of death included coronary artery disease (OR: 4.6; 95% CI: 1.4, 14.5) and immunocompromising conditions (OR: 5.0; 95% CI: 1.6, 15.7). Based on the results of this study, there was no difference in the outcomes (ie, survival, hospital length of stay, and discharge to a higher level of care) of patients who did and did not receive pneumococcal vaccination (Chi *et al*, 2006).

Pneumococcal vaccination rates among the elderly range from 49.9% among those aged 65 to 74 years to 60.9% among those aged 75 years and older (CDC, 2001b). Controversy over the clinical efficacy of the pneumococcal polysaccharide vaccine has been hypothesized as the number one reason for such low vaccination rates Butler *et* al, 1993; Fedson *et al*, 1994; Hirschmann *et al*, 1994). The most common manifestation of pneumococcal infection among the

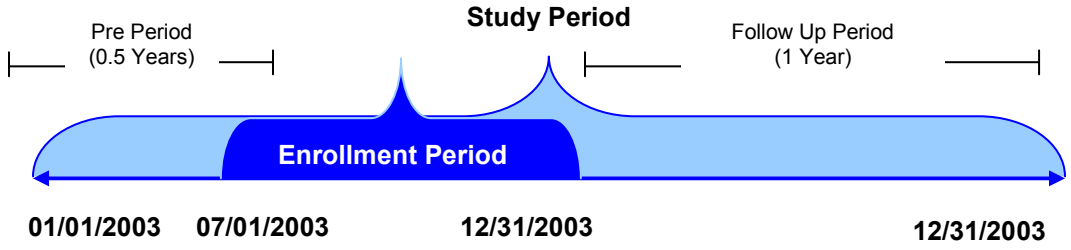
elderly is nonbacteremic pneumonia (Jackson *et al*, 2003). In patients with nonbacteremic pneumonia the vaccine failed to confer protection (Jackson *et al*, 2003) but was associated with a reduction in hospital LOS and death due to any cause (Fisman *et al*, 2006). The protective efficacy of the vaccine in preventing invasive pneumococcal infection (ie, bacteremia, meningitis, and infection of other normally sterile fluids) in U.S. elderly adults ranges from 61% to 75% (Sims *et al*, 1988; Shapiro *et al*, 1991; Butler *et al*, 1993). In U.S. elderly patients with pneumococcal bacteremia, there was no difference in outcomes (ie, all-cause mortality, hospitalization, and hospital LOS) between those who did and did not receive the vaccine (Chi *et al*, 2006).

CHAPTER TWO

Methods

In this retrospective cohort study, Medicare beneficiaries 65 years of age were assessed over a 2-year period, January 2003 through December 2004 (Figure 2). By nature of the study design, patients were selected based on their exposure status. Exposure was defined as receipt of the 23-valent pneumococcal polysaccharide vaccine, PPV23, (identified by *Current Procedural Terminology* [CPT] code 90736).

Figure 1. Study Design



Medicare beneficiaries with evidence of PPV23 administration during the enrollment period (July 1, 2003 through December 31, 2003) were matched to individuals with no documented receipt of PPV23 based on gender and the presence of any comorbidity. Only those aged 65 years of age in 2003 were included in the analysis to reduce the risk that the comparison group had been vaccinated prior to the enrollment period. Any comorbidity was defined as those conditions associated with high risk for the development of pneumococcal infection as defined by ACIP (Table 2). The study protocol was approved by the investigational review boards of the Centers for Medicare and Medicaid Services (CMS) and the University of South Florida and is in compliance with Health Insurance Portability and Accountability Act (HIPAA) regulations.

Table 2. ACIP PPV Recommendations

Comorbid Conditions of Interest: ICD-9 Codes
Alcoholism: 303.1-303.3, 303.9
Asplenia: 759.0
Cerebrospinal Leak: V45.2
Diabetes Mellitus (DM): 250, 250.0-250.9
Chronic Pulmonary Disease Emphysema, Bronchitis, Asthma: 490-496 Pneumocomycoses due to external agent: 500-505
Chronic Liver Disease Cirrhosis: 571.0-571.3, 571.5-571.6, 571.8, 571.9 Chronic Hepatitis: 571.4, 571.40, 571.41, 571.49
Human Immunodeficiency Virus (HIV): V07-V09, 042, 079.51-079.53
Immune Deficiency: 279.0, 279.00-279.06, 279.09, 279.1, 279.10-279.13, 279.19, 279.2, 279.3
Cardiovascular Heart Disease: 420-429, 429.0-429.3, 429.8, 429.9 Myocardial Infarction: 410, 412 CHF: 428, 425, 402.01, 402.11, 402.91
Cerebrovascular Disease: 434, 435, 436, 437, 438

Key: ACIP – Advisory Committee on Immunization Practices

Data Source

The data source for this study was the Medicare 5% beneficiary encrypted files (BEF) for the most recent two-year period from 2003 to 2004; available from CMS. The BEF represents a random 5% sample of the entire Medicare population which essentially includes all U.S. residents age 65 and older as well younger age groups who may qualify for Medicare due to a diagnosis of end stage renal disease (ESRD) or certain disabilities. The BEF data includes Durable Medical Equipment (DME), Inpatient Facility, Hospice, Outpatient Facility, Home Health Agency (HHA), Skilled Nursing Facility (SNF), and Physician / Supplier (Part B) claims. This analysis is conducted using claims from the Inpatient Facility, Outpatient Facility, and Physician / Supplier files.

Study Population

Beneficiaries enrolled in Medicare Parts A and B between January 1, 2003 and December 31, 2004 were included in the study. The current milestone for interventions to

prevent disease or to screen for asymptomatic disease is age 65 years. As such, in an attempt to assure no prior receipt of the pneumococcal vaccine, the study was further limited to patients who were age 65 years in 2003. Beneficiaries aged less than or greater than 65 years were excluded from the study.

Outcomes

The primary outcome was pneumonia, identified on the basis of *International Classification of Diseases, Ninth Revision; Clinical Modification* (ICD-9 CM) codes (480 throught 486). The incidence rate of pneumonia was calculated as the number of new patients diagnosed with pneumonia divided by total person-years of follow-up for all patients at risk for developing pneumonia. The total number of patients at risk for developing pneumonia totaled 7,388 and they were followed up for 1 year; as such, there were 7,388 persons-years of follow-up for patients at risk for developing pneumonia. Pneumonia requiring hospitalization was also evaluated. The incidence rate of hospitalization due to pneumonia was calculated as the number of new patients with pneumonia requiring hospitalization (i.e., denoted as an inpatient visit in our claims data) divided by total person-years of follow-up for patients with pneumonia. From January 1, 2004 through December 31, 2004, a total of 443 patients were diagnosed with pneumonia; thus, there were 433 person-years of follow-up for persons at risk for pneumonia requiring hospitalization. Beneficiaries were followed up for a total of 1 year; thus, there were a total of 7,388 patient-years of follow-up. As a secondary objective, we also evaluated pneumonia hospitalization costs. Mean costs were derived as the total claim payment amount for each claim of beneficiaries with an inpatient claim for pneumonia divided by the total number of patients with an inpatient visit for pneumonia.

Statistical Analysis

Descriptive statistics such as mean, standard deviation (SD), frequency, and percentage were generated for demographic characteristics, comorbid conditions, and vaccine utilization patterns. The frequency of categorical variables was compared using Chi-squared (χ^2) or Fisher's exact test. Mantel-Haenszel chi-square or logit was used to estimate the relative risk (RR) associated with vaccine exposure and outcome (ie, pneumonia and hospitalizations due to

pneumonia). Means were compared using Proc Ttest for equal variance. The alpha level for declaring statistical significance was *P* value <0.05. Data were analyzed using Statistical Analysis Software (Version 9.1, SAS Institute, Inc., Cary, North Carolina).

CHAPTER THREE

Baseline Characteristics

The cohort consisted of 7,388 persons who were followed up for 1 year (7,388 person-years), 3,694 (50%) received the pneumococcal vaccine during the enrollment period (July 1, 2003 through December 31, 2003). A majority (55.1%) was female, the most common documented race was Caucasian, and nearly 50% of all patients had one or more predisposing comorbidity (Table 4). The most common comorbidities, occurring in ≥10% of patients, were cardiovascular disease and chronic pulmonary disease. Less than 1% of the vaccinated and unvaccinated resided in a LTCF.

Table 3. Baseline Characteristics

Characteristic	Vaccinated (N=3,694)	Non-vaccinated (N=3,694)	*P* value
Gender, n (%)			
Female	2,035 (50.0)	2,035 (50.0)	1.000
Male	1,659 (50.0)	1,659 (50.0)	
Race, n (%)			
African American	192 (5.2)	369 (9.99)	<0.001
Caucasian	3,407 (92.2)	3,147 (85.2)	
Hispanic	17 (0.46)	36 (0.97)	
Other	270 (2.12)	142 (3.84)	
Comorbidities, n (%)			
Any Comorbidity	***1,704 (46.3)***	***1,704 (46.1)***	***1.000***
Alcoholism	7 (0.19)	30 (0.81)	<0.001
Asplenia	1 (0.03)	0 (0.00)	0.500
Cardiovascular	768 (20.8)	611 (16.5)	<0.001
Cerebrovascular	170 (4.60)	157 (4.25)	0.462
Cerebrospinal Leak	0 (0.00)	0 (0.00)	N/A
Chronic Liver Disease	44 (1.19)	43 (1.16)	0.914
Chronic Pulmonary Disease	637 (17.2)	527 (14.3)	<0.004
HIV	1 (0.03)	1 (0.03)	0.500
Immune Deficiency	5 (0.14)	1 (0.03)	0.094
Resides in LTCF, n (%)			
No	3,681 (99.7)	3,678 (99.6)	0.577
Yes	13 (0.35)	16 (0.43)	

Key: N/A – not applicable

Of the 3,694 patients with documented receipt of the vaccine, a majority (78.28%) was vaccinated during a physician office visit to a non-institutional provider. Of the remainder, 0.28% (n=103) of patients were vaccinated while at a hospital outpatient department, rural health clinic, renal dialysis facility, outpatient rehabilitation facility, comprehensive outpatient rehabilitation facility, community mental health center, or ambulatory surgical center. The remaining 21.52% (n=795) were vaccinated at some other healthcare facility. The most common provider specialty administering the vaccine was Internal Medicine (33.96%) followed by Family Practice (31.51%) and a Public Health or Welfare Agency (11.50%). Table 4 outlines the specialty distribution for providers administering the vaccine.

Table 4. Provider Specialty Distribution

Specialty	Frequency	Percent
Internal Medicine	1,332	33.96%
Family Practice	1,236	31.51%
Public Health or Welfare Agency	451	11.50%
Pulmonary Disease	107	2.73%
Other	357	9.13%

The recommended frequency for pneumococcal vaccination is once in a lifetime; unless however 5 years lapse between when a patient is vaccinated for the first time and their 65th birthday (DHHS, 1997). Despite these recommendations, a total of 181 patients (4.9%) were revaccinated within 1 year of their primary vaccination.

Outcomes

Pneumonia Disease Incidence

A total of 443 patients were assigned an ICD-9-CM code for pneumonia (codes 480 through 486); of which, 266 patients were previously vaccinated and 177 had no documented receipt of prior vaccination. This equates to an incidence rate of 36.0 per 1,000 person-years for the vaccinated and 24.0 per 1,000 person-years for the non-vaccinated. Results of the Chi-square analysis revealed a significant association between vaccination and the risk of pneumonia (*P* value <0.0001). The vaccinated were 50% more likely to develop pneumonia than were the

non-vaccinated (Adjusted RR: 1.50; 95% CI: 1.25, 1.81). The results of this analysis are summarized in Table 5.

Pneumonia Requiring Hospitalization

Of the 443 patients diagnosed with pneumonia, approximately 67.2% (n=298) required treatment within the hospital setting. Of the patients with pneumonia requiring hospitalization, 183 were previously vaccinated and 115 had no documented receipt of prior vaccination. The incidence of pneumonia requiring hospitalization in the vaccinated was almost 2.0-times that of the unvaccinated (41.3 per 100 person-years versus 26.0 per 100 person-years). Results of the Chi-square analysis failed to reveal a significant association between vaccination and pneumonia requiring hospitalization (*P* value 0.401). The results of this analysis are summarized in Table 5.

Table 5. Incidence and Risk of Pneumonia and Pneumonia Requiring Hospitalization in Relation to Vaccination Status

	Pneumonia (ICD-9-CM codes 480 – 486)	
Variable	**Disease**	**Hospitalization**
Adjusted rate*	Per 1,000 person-years	Per 100 person-years
Vaccinated	36.0	24.8
Non-vaccinated	24.0	15.6
Mantel-Haenszel relative risk (95% CI)	1.50 (1.25, 1.81)	1.06 (0.93, 1.21)
P value	<0.001	0.401

*Risk ratios were adjusted for sex and the presence of any comorbidity.

Pneumonia Hospitalization Costs

Among this study population of vaccinated (n=183) and non-vaccinated (n=115) Medicare beneficiaries aged 65 years, the vaccine was associated with significant reduction in mean hospital costs (*P* value 0.004). Hospitalization due to pneumonia ranged from $2,361 to $3,553 per admission for vaccinated patients and from $3,479 to $5,663 per admission for non-vaccinated patients and from; the average cost per admission for the vaccinated and non-vaccinated was $2,957 and $5,663, respectively. Because claim payment amounts for the non-vaccinated ranged from $0 to $90,419, we re-ran the analysis excluding those persons with claim payment amounts of $0 (n=16, non-vaccinated persons). As a result, the minimum claim payment amount for the non-vaccinated changed from $0 to $16 and the mean cost per hospital

admission for the non-vaccinated increased by $343 to $6,006. The results of this analysis remained significant (*P* value 0.001) and are summarized in Table 6.

Table 6. Pneumonia Hospitalization Costs in Relation to Vaccination Status

	Pneumonia Hospitalization Costs		
Vaccination Status	**Mean (95% CI)**	**Range**	***P* value**
All Persons Hospitalized for Pneumonia			
Vaccinated (n=183)	$2,957 ($2,307, $3,553)	$6 - $31,046	0.004
Non-vaccinated (n=115)	$5,663 ($3,479, $7,846)	$0 - $90,419	
Minus Persons with Claim Payment Amounts = $0			
Vaccinated (n=183)	$2,957 ($2,307, $3,553)	$6 - $31,046	0.001
Non-vaccinated (n=99)	$6,006 (3$,705 - $8,306)	$16 - $90, 419	

CHAPTER FOUR

Discussion

In this retrospective cohort study of 7,388 Medicare beneficiaries aged 65 years, vaccinated persons were 50% more likely to develop pneumonia than were non-vaccinated persons (*P* value <0.001). Despite controlling for the presence of any comorbidity, it is possible that residual confounding influenced our estimates of association between vaccination and risk of pneumonia. These results are not surprising as the vaccinated group was comprised of more immunocompromised patients than the non-vaccinated group; 21% versus 17%, respectively, for cardiovascular disease and 17% versus 14%, respectively, for chronic pulmonary disease (*P* value <0.001 for both comorbidities). Similar to other studies, we assume that *S. pneumoniae* was a common cause of pneumonia in this population (Jackson *et al*, 2003). Based on this assumption and our presumption of residual confounding, we can not conclude from these results that vaccination is not effective in preventing pneumococcal pneumonia. The direction of the association between vaccination and risk of pneumonia for this study (Adjusted RR: 1.50; 95% CI: 1.25, 1.81) is similar to the direction of the association between vaccination and outpatient pneumonia (Adjusted HR: 1.04; 95% CI: 0.96, 1.13) found in the retrospective cohort study conducted by Jackson *et al* (2003). Despite having 98% power to detect a 15% change in the risk of outpatient pneumonia and vaccination, Jackson and colleagues failed to detect such a decrease in risk (Jackson *et al*, 2003).

The results of our second analysis are consistent with the population based-case series study conducted by Chi *et al* (2006), which concluded that there was no evidence that the vaccine is associated with a reduction in the risk of hospitalization (Chi *et al*, 2006). In a retrospective cohort study conducted by Jackson *et al* (2003), the vaccine was associated a significant increase in risk of hospitalization for CAP; the vaccinated were 14% more like to be hospitalized for CAP than were the non-vaccinated (Adjusted HR: 1.14: 95% CI: 1.02, 1.28) (Jackson *et al*, 2006). In the same study, the vaccinated were found to be 6% more likely to be

discharged from the hospital with a diagnosis of pneumonia than were the non-vaccinated; however, the results of this analysis did not reach statistical significance (Adjusted HR: 1.06; 95% CI: 0.98, 1.16) (Jackson *et al*, 2006). Despite there being no difference in the rate of pneumonia requiring hospitalization among the vaccinated versus the non-vaccinated, our study suggests that there is a difference in hospital costs.

To date, no other study has looked at pneumonia hospitalization costs among vaccinated and non-vaccinated Medicare beneficiaries. On average, hospital admission costs for the vaccinated Medicare beneficiaries with pneumonia were $2,705 less than hospital admission costs for non-vaccinated beneficiaries (*P* value 0.004). Claim payment amounts ranged from $0 to $90,219 for the non-vaccinated and from $6 to $31,046 for the vaccinated; the upper limit of the claim payment amount range for the non-vaccinated was nearly three-times that of the vaccinated. This difference in magnitude may be due to the presence of outliers or longer hospital stays. Because we feel it is impossible to be hospitalized for pneumonia and not to incur costs, we re-ran our analysis excluding the 16 non-vaccinated persons with claim payment amounts of $0. The vaccine was still associated with a significant reduction in hospital costs; the difference in mean costs increased from $2,705 to $3,049 (*P* value <0.001).

In an attempt to understand why such low rates of pneumococcal immunization exist among older adults, we investigated the circumstances surrounding the administration of the vaccine to identify the provider specialties most frequently administering the vaccine and to quantify the proportion of patients revaccinated within 1 year of primary vaccination. Based on the results of our analysis, the most common provider specialties administering the vaccine was Internal Medicine (33.96%) and Family Practice (31.51%). Because such a large percentage of patients suffer from comorbid conditions of the pulmonary and cardiovascular systems, pulmonary disease and cardiovascular disease specialists should be administering the vaccine at much higher rates than those observed in this study; only 2.63% of the patients in our study were administered the vaccine by a pulmonary disease specialist. The ACIP recommended vaccination frequency for *S. pneumoniae* is once in a time lifetime; revaccination is recommended for those persons aged 65 years who received their primary vaccination ≥5 years previously. In

our study, a total of 181 patients (4.9%) were revaccinated within 1 year of their primary vaccination. Further investigation is warranted to distinguish true revaccination from duplicate claims. We were not able to investigate this issue due to the limitations of our data.

Limitations

Much like other observational studies, this study is subject to the limitation of a nonrandomized study design (Jackson *et al*, 2003). The primary source of these data was the CMS administrative claims database. As such, ascertainment of medical conditions (ie, pneumonia and other chronic medical conditions) and/or procedures (ie, pneumococcal vaccination) is subject to some degree of misclassification as the claims data are only as good as the person entering claims for adjudication (Jackson *et al*, 2003). Additionally, date variables in the CMS administrative claims database are formatted as 8 digit numeric variables denoting month, quarter, and year (ie, MMQQYYYY). As such, we could not further investigate revaccination rates or the possibility of outliers among our claim payment amounts for the non-vaccinated.

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APPENDICES

Appendix A: Studies of Pneumococcal Vaccine Effectiveness in Older Adults

Reference / Study Dates	Study Population / Infection Type	Study Design / Vaccine Valence	Key Primary / Secondary Endpoints	Results
Sims *et al*, 1988* **Study Dates** Not Reported	**Study Population** • Hospitalized immunocompetent >55 yrs **Infection Type** • Invasive Infection**	**Study Design** • Case Control (N=366) ▪ Cases, n=122 ▪ Controls, n=244 **Vaccine Valence** • PPV14 or PPV23	There was no distinction between primary and secondary endpoints • Invasive Infection**	<u>Invasive Infection</u> OR: 0.30 1- OR: 0.70 95% CI: 0.37, 0.86
Shapiro *et al*, 1991* **Study Dates** Not Report	**Study Population** • Patients admitted to one of 11 participating hospitals in Connecticut, USA • Subgroup of Interest: Immunocompetent 65-74 yrs **Infection Type** • Invasive Infection**	**Study Design** • Case Control (N=2,108) ▪ Cases, n=1,054 ▪ Controls, n=1,054 **Vaccine Valence** • PPV14 or PPV23	There was no distinction between primary and secondary endpoints • Vaccination Rates • Invasive Infection**	<u>Vaccination Rates</u> Cases: 13% Controls: 20% *P* value <0.001 <u>Invasive Infection</u> (Immunocompetent 65-74 yrs) OR: 0.39 1 – OR: 0.61 95% CI: 0.47, 0.72
Butler *et al*, 1993 **Study Dates** May 1978 – April 1992	**Study Population** • Patients with pneumococcal bacteremia and/or meningitis at institutions participating in the national pneumococcal	**Study Design** • Indirect cohort (N=2,827) ▪ Unvaccinated, n=515 ▪ Vaccinated, n=2,322 **Vaccine Valence**	**Primary** • Bacteremia and/or Meningitis • Protection Duration	**Primary** <u>Bacteremia and/or Meningitis</u> (Immunocompetent ≥65 yrs) OR: 0.25 1- OR: 0.75 95% CI: 0.57, 0.85

Reference / Study Dates	Study Population / Infection Type	Study Design / Vaccine Valence	Key Primary / Secondary Endpoints	Results
	surveillance program • Subgroup of Interest: Immunocompetent ≥65 yrs **Pneumococcal Infection Type** • Bacteremia and/or Meningitis	• PPV14 or PPV23		<u>Protection Duration</u> (Overall Study Population) <2 yrs: 51% (22%, 69%) 2 – 4 yrs: 54% (28%, 70%) 5 – 8 yrs: 71% (24%, 89%) ≥9 yrs: 80% (16%, 95%)
Farr *et al*, 1995 **Study Dates** January 1, 1981 – December 31, 1987	**Study Population** • Patients aged ≥2 yrs with pneumococcal bacteremia and chronic illness or those aged ≥65 yrs **Infection Type** • Bacteremia	**Study Design** • Case Control ▪ Cases, n=85 ▪ Controls, n=152 **Vaccine Valence** • PPV14 or PPV23	**Primary** • Bacteremia	<u>Bacteremia</u> (Overall Population) OR: 0.19 1- OR: .81 95% CI: 0.34, 0.94
CDC, 2001c **Study Dates** April 3 – 24, 2001	**Study Population** • Residents of a nursing home in New Jersey, USA **Infection Type** • Bacteremic Pneumonia	**Study Design** • Nested Case Control (N=23) ▪ Cases, n=9 ▪ Controls, n=18 **Vaccine Valence** • PPV23	There was no distinction between primary and secondary outcomes • Bacteremic Pneumonia	<u>Bacteremic Pneumonia</u> OR: 0 95% CI: 0.0, 0.7
Jackson *et al*, 2003 **Study Dates**	**Study Population** • Members of Group Health Cooperative in	**Study Design** • Retrospective Cohort (N=47,365)	**Primary** • Hospitalization for CAP	**Primary** <u>Hospitalization for CAP</u> (rate per 100,000 person yrs)

Reference / Study Dates	Study Population / Infection Type	Study Design / Vaccine Valence	Key Primary / Secondary Endpoints	Results
March 1, 1998 – February 28, 2001	Washington State ≥65 yrs **Pneumococcal Infection Type** • CAP • Pneumococcal Bacteremia	▪ Unvaccinated, n=21,052 ▪ Vaccinated, n=26,313 **Vaccine Valence** • PPV23	• Outpatient Pneumonia • Pneumococcal Bacteremia **Secondary** • Hospitalization with a Pneumonia Discharge Dx	Unvaccinated: 10.4 Vaccinated: 11.8 Adjusted HR: 1.14 95% CI: 1.02, 1.28 <u>Outpatient Pneumonia</u> (rate per 100,000 person yrs) Unvaccinated: 23.2 Vaccinated: 25.7 Adjusted HR: 1.04 95% CI: 0.96, 1.13 <u>Pneumococcal Bacteremia</u> (rate per 100,000 person yrs) Unvaccinated: 0.68 Vaccinated: 0.38 Adjusted HR: 0.56 95% CI: 0.33, 0.93 **Secondary** <u>Hospitalization with a Pneumonia Discharge Dx</u> (rate per 100,000 person yrs) Unvaccinated: 18.8 Vaccinated: 19.9 Adjusted HR: 1.06 95% CI: 0.98, 1.16 <u>All-cause Mortality</u>

Reference / Study Dates	Study Population / Infection Type	Study Design / Vaccine Valence	Key Primary / Secondary Endpoints	Results
				(rate per 100,000 person yrs) Unvaccinated: 50.1 Vaccinated: 42.0 Adjusted HR: 0.96 95% CI: 0.91, 1.01
Fisman *et al*, 2006 **Study Dates** September 1999 – December 2003	**Study Population** • Adults hospitalized with CAP **Infection Type** • CAP	**Study Design** • Population-Based Case Series (N=62,918) **Vaccine Valence** • PPV23	There was no distinction between primary and secondary outcomes • All-cause mortality • Adverse Events (other than in-hospital death) • Hospital LOS	<u>All-cause mortality</u> (Overall Population) OR: 0.29 95% CI: 0.26, 0.33 <u>Adverse Events (other than in-hospital death), OR (95% CI)</u> ARD: 0.67 (0.59, 0.76) Tracheostomy: 0.49 (0.33, 0.73) Acute renal failure: 0.55 (0.46, 0.65) Sepsis Syndrome: 0.74 (0.61, 0.90) Cardiac Arrest: 0.55 (0.46, 0.65) <u>Hospital LOS</u> Unvaccinated: 6.5 days Vaccinated: 4.5 days Unknown Status: 5.5 days *P* value <0.001 for pairwise comparisons by log rank test

Reference / Study Dates	Study Population / Infection Type	Study Design / Vaccine Valence	Key Primary / Secondary Endpoints	Results
Chi *et al*, 2006 **Study Population** 1988 – 2002	**Study Population** • Community-dwelling patients >65 yrs with at least 2 yrs enrollment in Group Health Cooperative **Infection Type** • Pneumococcal Bacteremia	**Study Design** • Population-Based Case Series (N=200) **Vaccine Valence** • PPV23	There was no distinction between primary and secondary outcomes • All-cause Mortality • Hospitalization • ICU Admission • Hospital LOS • Discharge to Home Care • Discharge to Nursing Home	<u>All-cause Mortality</u> Unvaccinated: 10.0% Vaccinated: 11.3% *P* value 0.78 <u>Hospitalization</u> Unvaccinated: 90.0% Vaccinated: 88.8% *P* Value 0.78 <u>Hospital LOS</u> Unvaccinated: 7.4 days Vaccinated: 5.7 days *P* Value 0.11 <u>Discharge to Home Care</u> Unvaccinated: 25.0% Vaccinated: 19.7% *P* Value 0.24 <u>Discharge to Nursing Home</u> Unvaccinated: 19.4% Vaccinated: 19.7% *P* Value 0.24

Key: ARD – acute respiratory distress, CAP – community-acquired pneumonia, CI – confidence interval, Dx – diagnosis, HR – hazard ratio, ICU – intensive care unit, LOS – length of stay, PPV – pneumococcal polysaccharide vaccine, OR – odds ratio, yrs – years, USA – United States of America
*Summarized from abstract as full manuscript was not available due to the date published.
**Invasive infection was defined as a diagnosis of pneumococcal pneumonia, meningitis, or any other bacteriologically confirmed pneumococcal infection.

Appendix B: Abbreviations

ACIP – Advisory Committee on Immunization Practices

ARD – acute respiratory distress

BEF – beneficiary encrypted files

CAP – community-acquired pneumonia

CDC – Centers for Disease Control and Prevention

CI – confidence interval

CMS – Centers for Medicare and Medicaid Services

CPT - Current Procedural Terminology

DME – durable medical equipment

Dx - diagnosis

ESRD – end stage renal disease

HHA – Home Health Agency

HR – hazard ratio

ICD-9-CM - International Classification of Diseases, Ninth Revision; Clinical Modification

ICU – intensive care unit

LOS – length of stay

LTCF – long term care facility

OR – odd ratio

PPV14 – 14-valent pneumococcal polysaccharide vaccine

PPV23 – 23-valent pneumococcal polysaccharide vaccine

SNF – skilled nursing facility

yrs – years

U.S. – United States

USA – United States of America