Trends and Surveillance of Adult Pneumococcal Diseases in Arkansas State, 2000 to 2013

by

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A dissertation submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
(Epidemiological Science)
in the University of Michigan
2016

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Dedication

To the best of people, my Mother and Father.

Acknowledgements

This dissertation would not have been possible without the support and guidance from my committee members: Dr. Zhenhua Yang, Dr. Carl Marrs, Dr. Wen Ye, Dr. Eden Wells and Dr. Jennifer Dillaha, whom I am deeply grateful for their dedication and genuine interest in my research. I am especially thankful to Dr. Jennifer Dillaha for allowing me to take advantage of this valuable opportunity and all her efforts in moving this research forward.

I am also grateful to the many individuals at the Arkansas Department of Health who I had the pleasure to work with and who continually supported me in acquiring the necessary data for my research and additional data pertaining to the public health situation in Arkansas, especially Carl Long, Lynda Lehing, Betty Bohanna, Dr. Haytham Safi, and Lucy Im. Very special thanks go to Marwa Saddawi for her hard work in extracting the data necessary for this work and for her great efforts in producing the matched data set needed for the sensitivity analysis. Rachel Guiquelais provided important guidance into the data matching procedure and surveillance system assessment. Dr. Dirk Haselow, the Arkansas state epidemiologist, contributed his expert knowledge in the interpretation of results.

I would also like to acknowledge my gratitude for the statistical help I received from Dr. Shyamala Nagaraj, Dr. Brenda Gillispie and Dr. Kerby Shedden at the University of Michigan's Center for Statistical Consulting and Research from.

Of special mention are Dr. Marc Ammerlaan and Dr. Paul Dunlap for hiring me as a graduate student instructor semester after semester and thus, allowing me to fund my doctoral

education and for sharing their valuable insights on pedagogy. I would also like to thank my fellow graduate student instructors and my students for always keeping me company.

This work was partly supported by generous grants and fellowships from the School Public Health and the Rackham Graduate School.

Finally, my deepest appreciation goes to my family, especially my parents and my husband for their all their love and support in this long process.

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List of Abbreviations (In alphabetical order)

ACIP	Advisory Committee on Immunization Practices
ADH	Arkansas Department of Health
ABCs	Active Bacterial Core Surveillance
CAP	Community-Acquired Pneumonia
CDC	Centers for Disease Control
ICD-9-CM	International Classification of Diseases, 9th Revision, Clinical Modification
IPD	Invasive Pneumococcal Disease
PD	Pneumococcal Diseases
PP	Pneumococcal Pneumonia
HDD	Hospital Discharge Data
MSA	Metropolitan Statistical Areas
NB	Negative Binomial
NBS	NEDSS Base System
NEDSS	National Electronic Disease Surveillance System
NETSS	National Electronic Telephonic System for Surveillance
NHIS	National Health Interview Survey
PPSV23	23-valent pneumococcal polysaccharide vaccine
PCV7	Prevenar 7
PCV13	Prevenar 13
VA	Veteran Affairs
US	United States

Abstract

Pneumococcal diseases have high mortality and morbidity worldwide, and they present in two major clinical manifestations: 1) pneumococcal pneumonia, which is the most common manifestation and 2) invasive pneumococcal disease that is less frequent but more often fatal. Pneumococcal diseases disproportionately affect young children and the elderly. The population of Arkansas is highly vulnerable due to high rates of chronic diseases, a rapidly aging population and low adult vaccinations rates. This dissertation aims at understanding the epidemiology of adult pneumococcal pneumonia and adult invasive pneumococcal disease in the state of Arkansas during the past 14 years to inform future immunization program improvement. Additionally, the sensitivity and completeness of the adult invasive pneumococcal disease surveillance system during 2003 to 2013 were assessed to evaluate the usefulness of surveillance data in informing immunization planning. Records of adult pneumococcal pneumonia and invasive pneumococcal disease cases with de-identified demographic information were extracted from hospital discharge data. Overall and subpopulation trends were evaluated using generalized linear models. Pneumococcal pneumonia trends displayed a gradual annual percent decline of 5.07% per year (95% CI: 3.53, 6.95) from 2000 to 2009. The decline became more pronounced from 2010 to 2013 at 19.10% per year (95% CI: 14.10, 23.51). On the other hand, the IPD trends showed a small annual percent increment of 3.66% per year (95% CI: 2.02, 4.92) from 2000 to 2009, followed by a decline of 11.31% per year (95% CI: 15.46, 6.57) from 2010 to 2013. Subpopulation trends showed similar trend patterns. These results highlight the indirect effects of

the introduction of childhood vaccinations PCV7 in 2000 and PCV13 in 2010 on the reduction of the pneumococcal disease burden among adults. The surveillance system assessment revealed its low capacity for capturing adult invasive pneumococcal disease cases. However, a significant improvement in the sensitivity and data quality was observed over time, especially after the implementation of the web-based National Electronic Disease Surveillance System.

Chapter 1

Introduction

1.1. *Streptococcus pneumoniae* Infection and Pathogenesis

Streptococcus pneumoniae is a gram-positive bacterium that causes acute bacterial infections ranging from pneumonia, blood infections (sepsis or bacteremia), to meningitis, and they fall under the category of pneumococcal diseases (PD). Pneumococci have a polysaccharide layer surrounding their surface called a capsule. Capsules are the basis for the organisms' pathogenicity. Capsules are also antigenic and are used for classifying pneumococci into different serotypes. More than 90 serotypes have been identified, based on antibody-antigen reactions. Most *S. pneumoniae* serotypes have been shown to be pathogenic, but only a few of them cause the majority of pneumococcal infections. Pneumococci are part of human normal flora and are recovered from the nasopharynx of 5% to 10% of healthy adults. However, rates of asymptomatic carriage vary with age, environmental conditions, and the presence of upper respiratory infections. *S. pneumoniae* carriage provides the basis for future development of PD (1, 2).

S. pneumoniae is transmitted through coughing or sneezing, or through direct contact with an infected individual. The development of PD may be sudden, and depends on the type of infection. People may experience a combination of the following symptoms: fever onset, chills, cough, breath shortness, chest pain, stiff neck, disorientation, and sensitivity to light. Most of the burden of PD in adults is related to non-invasive disease, such as otitis media, sinusitis, and pneumococcal pneumonia (PP). Invasive pneumococcal disease (IPD) is much less common but

more often fatal and is defined as an infection confirmed by the isolation of *S. pneumoniae* from a normally sterile site, such as blood or cerebrospinal fluid that will manifest as sepsis, bacteremia or meningitis (1, 2).

1.2. Epidemiology of Pneumococcal Diseases

Pneumococcal infections kill tens of thousands of people in the United States (US) every year. PD displays a U-shape age distribution in which the eldest and youngest are most affected. Even though older people are more likely to die due to PD, younger adults with certain health conditions are also at increased risk for severe illness and death. Community-acquired pneumonia (CAP) is a highly prevalent condition in the general population of variable severity (2, 3, 4). In a large cohort study in the US, the incidence rate for CAP requiring hospitalizations was estimated to be 270 per 100,000 (5), and it was found to be the most frequent cause of death from infection, especially among the elderly (2, 3, 4). CAP may be caused by a number of different infectious agents, but *S. pneumoniae* is the most frequently identified pathogen (6, 7, 8). A European study identified *S. pneumoniae* as the causative agent in an average of 35% of CAP cases, ranging from 12% to 68% among various countries. Furthermore, this study found this to be true for all settings, including outpatients, hospital-treated patients and intensive care patients (6). In the US, as many as 175,000 cases of PP occur every year with a case fatality of five to seven percent which increases with age (7, 8).

In a study by Robinson et al. (8) composed 16,000 adult IPD cases in the US, the origin of infection was pneumonia in 53% of the cases, while in 40% of the cases bacteremia was diagnosed without a focus. Adult IPD incidence ranges from 3.8 per 100,000 among persons aged 18–34 years to 36.4 per 100,000 among those aged 65 years and older. The disease rates for immunocompromised adults and those with high-risk medical conditions can be as high as 324

per 100,000 with case-fatalities reaching up to 80 percent. However, IPD is also affected by other factors, such as genetic background, socioeconomic status, tobacco and alcohol use, and geographic location (9, 10).

1.3. Vaccination Interventions

Fortunately, vaccines do exist that are effective against preventing PD. In the 1980s, a vaccine containing purified capsular polysaccharides from 23 of pneumococcal serotypes (PPSV23) causing of 85 to 90 percent of adult IPD was introduced in the US (11). PPSV23 efficacy and effectiveness studies among persons in recommended target groups (the elderly and the immunocompromised) have yielded contradictory conclusions for pneumococcal pneumonia prevention. However, most studies have consistently demonstrated protection against IPD among healthy young adults and elderly adults. Observational studies have suggested effectiveness of PPS23 ranges between 50 and 80 percent for the prevention of IPD among immunocompetent older adults and adults with various underlying illnesses, which supports the recommendation for immunization using PPSV23 to prevent adult IPD. Despite available vaccines, vaccination rates among adults are low nationwide (11, 12).

In 2000, a pneumococcal conjugate vaccine containing capsular polysaccharides from seven serotypes (PCV7) targeted at children was licensed in the US (13). Studies demonstrated that the vaccine was effective at reducing IPD from vaccine serotypes in children. Also, an indirect benefit on adults was noted as a result of PCV7 vaccination which was a reduction of IPD rates by a range of 8 to 30 percent (13) and a significant decline in the proportion of adult pneumococcal pneumonia caused by PCV7 serotypes (14). This herd immunity effect was the result of PCV7 reducing the *S. pneumoniae* carriage rate among children, thereby reducing the circulation of serotypes included in the vaccine among adults (9, 15). In 2010, PCV13, which

includes all seven serotypes in PCV7 and six additional serotypes, was licensed for the prevention of IPD and ear infections in infants and young children, supplanting PCV7. In 2011, PCV13 was licensed to be used to prevent IPD in adults aged 50 years or older based on higher antibody titers when compared to adult responses using PPV23 (16). Currently, two pneumococcal vaccines are approved for use in adults in the U.S. for the prevention of adult IPD, PPSV23 and PCV13 (17).

The Advisory Committee on Immunization Practices (ACIP) recommends that high-risk adults of 19 to 64 years of age with immune-compromising conditions (including chronic renal failure and nephrotic syndrome), functional or anatomic asplenia, cerebrospinal fluid leaks, or cochlear implants and have not been previously vaccinated with PCV13 or PPSV23 to receive a dose of PCV13. A dose of PPSV23 should follow at least eight weeks later, and a one-time revaccination 5 years after the first dose of PPSV23 (17).

Additionally, the ACIP recommends that all individuals aged 65 and older should be administered PCV13 and PPSV23 routinely and in series. Adults aged 65 and older who have not previously received pneumococcal vaccine or whose previous vaccination history is unknown should receive a dose of PCV13 first, followed by a dose of PPSV23. The dose of PPSV23 should be given six months after a dose of PCV13. Adults 65 years and older who have previously received one or more doses of PPSV23 also should receive a dose of PCV13 if they have not yet received it. A dose of PCV13 should be given at least one year after the receipt of the most recent PPSV23 dose. For those who are recommended an additional dose of PPSV23, the subsequent PPSV23 dose should be given 6–12 months after PCV13 and at least 5 years after the most recent dose of PPSV23 (17).

1.4. Invasive Pneumococcal Disease Surveillance

In the US, requirements for reporting certain communicable or chronic diseases are mandated by state laws. Invasive *S. pneumoniae* disease has been reportable since 1996 (31). In 2001 all cases regardless of age or drug-resistance status became notifiable to the Centers for Disease Control (CDC) in the state of Arkansas (31). The Arkansas Department of Health (ADH) receives IPD reports from several sources, including hospitals, laboratories and clinics. Suspect cases are investigated and classified using the CDC 2010 case definition (Table 1.1). The ADH notifies the CDC of confirmed cases using the National Electronic Diseases Surveillance Systems (NEDSS) Base System (NBS), which was developed to improve public health monitoring of infectious diseases (31).

For most diseases, ascertainment rates in surveillance systems are low and should be used with caution. However, efficient and reliable surveillance systems are critically important for monitoring disease trends to guide immunization policies. Additionally, planning for interventions, such as immunizations and allocation of health services, are often based on the disease prevalence, incidence and morbidity estimates provided by surveillance systems (19). Previous studies have revealed limitations associated with the use of data from passive surveillance systems, because most of them are affected by a degree of underestimation (20, 21) that impacts estimates of "true" disease incidence. Infectious diseases that may present asymptomatically or that are self-limiting are considered particularly prone to being underrepresented in surveillance data (22). Thus, when routine data are used to inform decisions relating to allocation of health resources, or to estimate epidemiological parameters in a population, it becomes important to understand the limitations of that reporting system.

Underestimation of infectious events in surveillance systems may be community or healthcare related. At the community level, underestimation may occur when asymptomatic

individuals or those who experience a mild disease course do not seek care at a health care facility, and thus those cases cannot be captured by the surveillance system. At the health care level, underreporting may occur when the surveillance system is not notified by healthcare providers of sick individuals (22).

Underreporting at the health care level may also result from misdiagnoses, which may arise when biological samples are not requested by health professionals or provided by patients, when there are budget limitations with regard to testing, when the testing tools are inadequate, or when there is a lack of knowledge of which tests to perform. Underreporting may also result from lack of knowledge of when, how, or which diseases to correctly report (23, 24). More cases are reported when there are legal mandates to notify authorities (25), when there are incentives for healthcare workers to request and test biological samples from patients and to report results (23), and when there is a perceived sense of urgency, such as during outbreaks or for very rare diseases (26). Studies have also found that the urgency to report very serious conditions may be age- or sex-dependent (27, 28).

A review on communicable disease reporting completeness for a number of different infectious diseases in the US revealed a variable range of 9% to 99% of cases of notifiable diseases actually reported to public health authorities. High reporting rates were strongly associated with particular diseases, such as tuberculosis and HIV, which was attributed to perceived severity of conditions or conditions that are known to be costly to the health system (29). However, complex case definitions may also impact reporting. A recent study found that pertussis, a notifiable disease in the US, is largely underreported in Arkansas, with only 55% of hospitalized cases actually reported to the national surveillance system (30).

1.5. Population of Arkansas

The study population for this dissertation is the adult Arkansas state population. The state of Arkansas has a population of about 3 million. Adults (18 years and over) compose 75% of the population and 65 years and older make up 14% of the total population which is similar to the proportion in the entire US population. However, the number of adults over 60 years of age is on the rise and it is speculated that by 2030 there will be more individuals over 60 years than under 60 years of age and older. The male to female ratio is 1:1.03. The majority of the population is White (75%), however Blacks make up 15% of the population. There is also a significant proportion of Latinos of about 6%, making them the largest minority ethnic group (31).

The population of Arkansas is ranked low in terms of overall health (48th out of 50) and has a lower life expectancy than the US life expectancy (76 vs.78 years). The most common causes of death among adults in Arkansas include chronic diseases and accidents. The most frequent chronic diseases in this population include heart disease, cancer, chronic lung disease and kidney disease. High rates of chronic diseases have been attributed to poor diets, lack of physical activity and smoking behavior that lead to obesity and high blood pressure. In addition to chronic diseases this population is also heavily burdened by infectious diseases. Influenza and pneumonia are the eight most common causes of death while blood infections are tenth (31).

Racial health and economic disparities, especially between Blacks and Whites are very evident in the Arkansas population. Blacks have lower educational attainment and thus have higher unemployment rates than Whites. In 2010, 34.4% of Black were living in poverty compared to 14.4% of Whites. In terms of health, Blacks have greater chronic disease incidence and mortality than their White counterparts especially in heart disease, and in cancers such as cervical, colorectal and prostate. Blacks also have excessively high HIV mortality rates of 7.6 per 100,000 population compared to only 1.5 deaths per 100,000 White population (32).

Arkansas is made up of 75 counties. It is considered a largely rural state because about 50% of the population lives in rural areas compared to only 19% of people in the US. Rural populations are known to experience greater overall diseases burdens, have lower life expectancies and have greater proportions of people living in poverty than urban populations (31, 33). Additionally, rural areas have a greater concentration of people 75 years and older and Whites than urban areas. All of this highlights important health differences between urban and rural populations. Furthermore, rural areas suffer from poor access to health care services compared to urban areas. For example, in 2012 there were 64.5 primary care physicians per 100,000 population in rural areas of the state, compared to 139 per 100,000 in urban areas (33).

The population of Arkansas is a rapidly aging population with high rates of chronic diseases which places it at a very high risk for adult PD. Thus, this population could benefit greatly from improving adult vaccination rates. Understanding the epidemiology of adult pneumococcal disease in this population also necessitates the examination of how medically disadvantaged or underserved subpopulation groups are affected.

1.6. Research Initiatives

Many studies elucidating national PD trends using Active Bacterial Core Surveillance (ABCs) data have been released (9, 13). A recent study showed that IPD trends from 1998 to 2009 were highly variable according to geographic region (34). Thus, this dissertation set out to understand the epidemiology and trends of adult pneumococcal diseases in the population of Arkansas and to assess the impact of the introduction of conjugate vaccines in recent years. In Chapter 2, we examined the overall adult pneumococcal pneumonia trends as well as the subpopulation-specific trends using statewide Arkansas hospital discharge data from 2000 to 2013. In Chapter 3, we examined adult IPD overall and subpopulation specific trends during the

same time period. These are the first studies on adult pneumococcal disease trends in Arkansas. This work intended to provide a baseline understanding of the burden adult PD represents in this population in order to inform future immunization planning.

In line with reinforcing surveillance systems which are necessary to provide accurate epidemiologic data needed to design future immunizations, in Chapter 4, we assessed the functioning of the adult IPD surveillance system in Arkansas. Using adult IPD cases in hospital discharge data and in the surveillance system from 2003 to 2013, we examined sensitivity and completeness of the information that surveillance system provides.

1.7. Table

Table 1.1. Council of State and Territorial Epidemiologists (CSTE) Invasive pneumococcal 2010 case definition

Invasive Pneumococcal Disease (IPD, *Streptococcus pneumoniae*, invasive disease) Definition	
Clinical Description	*S. pneumoniae* causes many clinical syndromes, depending on the site of infection (e.g., acute otitis media, pneumonia, bacteremia, or meningitis).
Laboratory Criteria	Isolation of *S. pneumoniae* from a normally sterile body site (e.g., blood, cerebrospinal fluid, or, less commonly, joint, pleural or pericardial fluid)
Case Classification	**Suspected:** Any reported case lacking confirmation of isolation of *S. pneumoniae* from a normally sterile body site **Confirmed:** Isolation of *S. pneumoniae* from a normally sterile body site in a person of any age.

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Chapter 2

Adult Pneumococcal Pneumonia Trend in Arkansas State, 2000 to 2013

2.1. Introduction

Streptococcus pneumonia is a major cause of a wide range of diseases called PD, which have high morbidity and mortality especially among the elderly in the US and worldwide (1,2). PP is the most common clinical manifestation of PD. Approximately 400,000 hospitalizations are reported every year in the US. Adults with chronic conditions are at especially high risk (3). Additionally, this pathogen is the etiological agent of 30% to 50% of CAP cases (1,2). *S. pneumoniae* is normally found in the nasopharynx of young children. However, colonization wanes with adulthood, thus it is hypothesized that transmission occurs from children to adults (4).

Most *S. pneumoniae* contain a capsule composed of complex polysaccharides. The capsule determines pathogenicity and is the target for current and past vaccines (3). Even though there are 92 different serotypes based on differences in capsular polysaccharides, only a few of them are responsible for the majority of serious infections (3). There have been several vaccines against pneumococcal diseases introduced in the US in recent years. Since 1997, the ACIP has recommended a 23-valent pneumococcal polysaccharide vaccine (PPSV23) to all adults 65 years and older and individuals 2 to 64 years with conditions that put them at high risk (5). In 2000, a conjugate vaccine containing seven of the most prevalent disease-causing serotypes called Prevenar 7 (PCV7) was licensed and added to the childhood immunization schedule (6). In 2010,

another childhood conjugate vaccine, PCV13 (Prevnar 13, manufactured by Pfizer), which contains 6 additional serotypes replaced PCV7 (7). Conjugate vaccines effectively reduced pneumonia and acquisition of nasopharyngeal carriage of vaccine-type strains among children, and consequently decreased transmission to adults (8).

Despite recommendations to vaccinate older adults, and Medicare reimbursement incentives for vaccination, the national vaccination coverage has remained low (9). The most recent overall national pneumococcal vaccination coverage estimate from the 2013 National Health Interview Survey (NHIS) was 59.7% among adults 65 years and older (10). Multiple factors have been attributed to low adult vaccination rates including vaccine availability, attitudes towards vaccinations, and low propensity to seek vaccinations (9, 11). Adults of ethnic and racial minorities are known to have significantly lower vaccine coverage than their White counterparts (11).

Arkansas is ranked number 48th out of 50 states in terms of overall health and among the top ten leading causes of death for the Arkansas population are pneumonia and influenza. With high rates of chronic diseases, a large proportion of people living in rural areas with low access to health care services and with a rapidly aging population, the Arkansas adult population is at high risk for PD (12). The purpose of this study is to examine hospitalized PP trends from 2000 to 2013 among the adult population of Arkansas to understand the impact of childhood vaccinations and shed light on sub-populations that would most benefit from efforts to improve vaccination rates.

2.2. Methods

2.2.1. Study Population and Data Sources

The study sample comprised of all adults (18 years and older) hospitalized for

pneumococcal pneumonia in Arkansas from January 1, 2000 to December 31, 2013. The data were extracted from the Arkansas Hospital Discharge Data (HDD) System using International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes indicative of PP. A patient was included in the sample based on the following criteria: 1) a first listed diagnosis code for pneumococcal pneumonia (481), or 2), a first listed diagnosis for unspecified pneumonia (482.3, 482.39, 482.89, 482.9, 483.8, 486, and 487.0) with a second listed diagnosis code for *S. pneumoniae* infection (041.2). The study included all adult pneumococcal pneumonia cases that presented to any hospital. We excluded the two Veteran Affairs (VA) hospitals in Arkansas since information on VA patients is not included in the state's HDD.

De-identified data for each cases included demographics of age, gender, race and residence. The patient's residence was categorized as rural or urban. This classification was derived from the patient's address zip codes, using methods delineated by the Census Bureau Metropolitan Statistical Areas (MSAs) definitions from the Office of Management and Budget (13). Approval was received from the Institutional Review Board for Health Sciences and Behavioral Sciences at the University of Michigan and the Science Advisory Committee of the Arkansas Department of Health for this study.

2.2.2 Incidence Rate Calculations

In order to understand disease trends in Arkansas, annual PP hospitalization rates for the total population and subpopulations were calculated using the population estimates from the 2000 and 2010 US census (14). The 2000 population estimates were used to calculate incidence rates from 2000 to 2009 and the 2010 census population estimates were used for the 2010 to 2013 incidence rates. Confidence intervals for observed annual hospitalization rates were calculated by using a negative binomial regression model with time as a categorical variable.

2.2.3. Model Building

To assess the percent change in trends over time, we modeled the overall and subpopulation specific seasonal rates using negative binomial regression model with an offset for person-time using generalized linear models (GEE) methods. Poisson regression models were also attempted but were not a good model fit due to data over-dispersion. We made use of segmented regression by including a knot variable in the model at the time point in which the trends change to adjust for the time effect. Due to the strong seasonal component associated with PP incidence (15), we modeled the percent change in rate per season. Seasons were defined as: Winter (December through February), Spring (March through May), Summer (June through August) and Fall (September through November). The estimated percent seasonal changes were then transformed into annual percent changes in rates.

To compare the annual percent change in PP trends between different subpopulations of race (Blacks and Whites), gender (male and female) and residence (urban and rural), we used univariate negative binomial segmented regression with time interactions. For each analysis the model included one demographic variable, the segmented time variables and the interactions between time segments and the demographic variable. If a regression coefficient of the interaction terms was significantly different from zero, it indicated that the demographic variable was significantly associated with a percent decline in the rate of PP. Over 80% of cases found from 2000 to 2002 did not report race, thus all race analyses was limited to years 2003 to 2013. All models included categorical variables for season to adjust for the effect of seasonality. All analyses were stratified by age group: adults 18 to 64 years and 65 years and older because PP risk is strongly correlated with age and the current adult pneumococcal vaccine recommendation targets individuals 65 years and older (2, 3). All statistical analyses were performed using IBM

Statistics SPSS for Windows version 22 (IBM Corp., Armonk, N.Y., USA) (16). In all the analyses, p-values less than 0.05 were considered to be statistically significant.

2.3. Results

2.3.1. Characteristics of the Study Population

A total of 3,484 adult cases with an ICD-9 code indicative of pneumococcal pneumonia were reported in HDD in Arkansas during the study period (January 1, 2000 to December 31, 2013). The large majority of cases 3,424 (98.3%) had a first listed diagnosis code for PP. Although, there were equal proportion of males and females and urban and rural cases, the majority of cases were in the older age category of 65 years and older and of White race (Table 2.1).

2.3.2. Adult Pneumococcal Pneumonia Hospitalization Trends

The average adult PP annual hospitalization rate from 2000 to 2013 in Arkansas was 12.32 per 100,000 adults (95% CI 10.29, 14.59). Average annual rates demonstrate a sustained decline from 2000 to 2013 (Figure 2.1). Statewide adult PP hospitalization rate trends from 2000 to 2009 showed an annual percent decline of 5.07% per year (95% CI: 3.53, 6.95) (Figure 2.2). From 2010 to 2013, adult PP hospitalization rates also declined but at a significantly faster rate ($p<0.001$), by 19.10% per year (95% CI: 14.10, 23.51) (Figure 2.2). This significantly faster decline during 2010 to 2013 was also observed in all sub-population groups evaluated (age groups, gender, race, and residence) (Table 2.4a and 4b).

2.3.3. Comparisons of Pneumococcal Pneumonia trends between Adults 18 to 64 Years and 65 Years and Older

During the 14 years of observations, adult PP average annual hospitalizations rates were consistently higher in the older age group than the younger age group (Figure 2.3). As illustrated

in Figure 2.4, in 2000, those 65 years and older experienced 4.41 times (95% CI: 3.07, 5.02) higher pneumococcal pneumonia hospitalization rates than the younger age group. Both age groups demonstrated a decline in hospitalization rates for the entire study period (Figure 2.3). However, the older age group experienced a significantly greater decline than the younger age group. During 2000 to 2009 the annual decline in PP hospitalization rate among those 18 to 64 years was 3.53% (95% CI: 1.59, 5.44), while the rate for those 65 years and older declined by 6.57% (95% CI: 4.69, 8.42) (p-value for difference=0.015) (Figure 2.4). During 2010 to 2013 the estimated annual decline among those 18 to 64 years was 15.12% (95% CI: 9.52, 20.39), for those 65 years and older it was 22.58% (95% CI: 17.14, 27.38) (p-value for difference=0.032) (Figure 2.4). In 2013 the older age group experienced 3.51 times (95% CI: 2.52, 4.89) higher hospitalization rates than the younger age group (Figure 2.4).

2.3.4 Comparison between Male and Female Adult Pneumococcal Pneumonia Trends

Gender disparities have been observed for many diseases, thus we explored differences in male and female disease tend trajectories. For the age group 18 to 64 years, both males and females experienced similar PP hospitalization rates during the entire study period (Tables 2.2a and 2b). Furthermore, in this age group a similar and significant annual percent decline was observed for both genders during 2000 to 2009 and 2010 to 2013 (Tables 2.3a and 3b). The decline during the 2010 to 2013 was significantly greater than that during 2000 to 2009 ($p<0.001$) (Data not shown).

In contrast, at the beginning of the study period, females 65 years and older experienced 25% (95% CI: 10.0, 36.0) lower rates than males (Table 2.2a). Males and females 65 years and older experienced similar annual percent declines during the entire study period (Tables 2.3a and 3b). However by the end of study period in 2013, the difference between males and females was

no longer significant (Table 2.2b).

2.3.5 Comparison of Black and White Adult Pneumococcal Pneumonia Hospitalization Trends

Adult PP disease burden and trends between the two main racial groups in Arkansas (Blacks and Whites) were compared to understand pneumococcal pneumonia racial disparities. In 2003, Blacks and Whites aged 18 to 64 years experienced similar incidence rates (Table 2.2a). Blacks experienced a faster decline than Whites from 2003 to 2009 (9.88% vs. 3.53% per year) and from 2010 to 2013 (30.23% vs. 15.12% per year). However this difference was only significant in the second segment (p=0.036) (Table 2.3a and 3b). By the end of the study in 2013, Blacks experienced 59% (95% CI: 16.0, 80.0) lower rates than Whites (p=0.014) (Table 2.2b).

Unlike the younger age group, among those 65 years and older, Blacks experienced lower pneumococcal pneumonia hospitalization rates than Whites during the entire observation period (Tables 2.2a and 2.2b). Blacks also experienced a faster annual percent rate decline than Whites (2003-09: 10.24% vs. 5.45% and 2010-13: 31.87% vs. 21.02%). However the differences between percent rate declines in Blacks and Whites were not significant (Tables 2.3a and 3b).

2.3.6 Comparison of Urban and Rural Adult Pneumococcal Pneumonia Hospitalization Trends

Since almost half of the Arkansas population resides in rural areas (12), we compared disease burden and trends among rural and urban sub-populations. Throughout the study period, adults 18 to 64 years in rural and urban counties experienced similar annual rates (Table 2.2a and 2.2b). The percent annual decline in PP hospitalization rates from 2000 to 2009 were similar for urban and rural populations 18 to 64 years (Table 2.3a). However, during 2010 to 2013, rates in urban counties declined faster than rural counties but this difference was not statistically significant (19.75% vs. 13.76% per year) (Table 2.3b).

At the beginning of the study period, adults 65 years and older residing in rural counties were found to have 26.0% (95% CI: 6.0, 50.0) higher hospitalization rates than urban counties (Table 2.2a). Among adults 65 years and older, the decline in hospitalization rates from 2000 to 2009 was not significantly different for urban and rural populations (Table 2.3a). However, from 2010 to 2013, the annual percent decline in rural counties was greater in rural (25.62% 95% CI: 31.61, 19.10) than in urban (16.81% 95% CI: 22.89, 9.88) populations (p=0.038) (Table 2.3b). However, by year 2013, the difference in hospitalization rates between urban and rural was non-significant (p=0.337) (Table 2.2b).

2.4. Discussion

In order to understand adult pneumococcal pneumonia trends in Arkansas State and to identify disparities between subpopulations, this study made use of over 3,484 hospitalized pneumococcal pneumonia cases in HDD spanning the entire state and a 14 year study period. We identified a marked and steady decline in adult PP rates since 2000. Additionally, in 2010 the percent rate decline became more pronounced. These trends were also observed among all sub-population groups evaluated.

Declines in pneumonia rates among adults have been well documented in the literature as a result of herd immunity protection from routine administration of the conjugate pneumococcal vaccines among children in the U.S. (8, 17). Our study provides additional evidence for this positive impact by demonstrating a sustained and significant decline in adult pneumococcal pneumonia hospitalization rates in Arkansas. Age, sex, race, and residence group specific trends also demonstrated an evident decline. Interestingly, the percent annual decline during 2010 to 2013 was significantly higher than that from 2000 to 2009. This much more pronounced decline may be the result of changes in local and national vaccination policy changes. In 2007, the ACIP

revised its PCV7 recommendation to include all children ages 2 to 59 months despite any medical conditions. Prior to 2007, PCV7 supply was limited and thus only children at very high risk were recommended to receive the vaccine (18). Also in January of 2008, the Arkansas State Board of Health made it mandatory for all children attending day care to be vaccinated with PCV7 (19). Finally in February of 2010, the Food and Drug Association approved another conjugate pneumococcal vaccine in the US, PCV13. This 13-valent pneumococcal polysaccharide-protein conjugate childhood vaccine succeeded PCV7 (7). Changes in the administration of PCV-7 that went into effect in Arkansas and in the US along with the additional herd immunity provided by the introduction of PCV13 nation-wide may all contribute to the greater decline in hospitalization rates identified in this study during 2010 to 2013.

The age-stratified analyses revealed that the annual percent decline in PP hospitalization rates in adults 65 years and older was greater than that in adults 18 to 64 years of age. This result may reflect the positive impact of the recommendation to vaccinate all adults 65 years and older with PPS23 since February of 1997 (5). Although slow, the uptake of PPSV23 has been steadily increasing in the US and in Arkansas (20). In 2008, it was estimated that 64.2% of adults 65 years and older in Arkansas had received PPSV23 and in 2013 the percentage was estimated to be 67.3% (21). Adults 65 years and older are more likely to directly benefit from the additional protection of PPSV23. Adults 18 to 64 years who did not get the vaccine may not benefit, because this age groups is not included in the PPSV23 vaccine recommendation (5). Also, the greatest PP percent rate decline, and thus the greatest vaccine benefits, are expected in the eldest age group who is most affected by this disease.

Higher hospitalization rates among males 65 years and older were found at the beginning of the study. However, towards the end males and female rates became similar. A previous study

found that male sex was a risk factor for adult PD (22). Another study by the American Lung Association, using hospital discharge records in the US from 2000 to 2006, reported higher PP mortality rates for males than females (20). Despite finding differences in disease burden in this study, males and females in this age group did not show significantly different trend trajectories.

On the other hand, among adults 18 to 64 years, we found similar hospitalization rates for both sexes throughout the study period. This finding is congruent with other studies that have also shown that differences in CAP incidence between sexes are most evident in the older age groups (23). This age difference may have to do with access to pneumococcal vaccinations for different age groups. A recent study on adult immunization rates in 2012 in the US found that males and females in the 19 to 64 age range were equally likely to have received pneumococcal vaccinations, while for adults 65 years and older, females were 10% more likely to have received pneumococcal vaccinations compared to males (24). Thus, among those 65 years and older in Arkansas, females may be better protected against pneumococcal infections and thus experience lower hospitalization rates than males.

Despite known racial health disparities in Arkansas, in this study Blacks in all age groups and throughout the entire study period experienced greater annual percent declines and lower hospitalization rates than their White counterparts. This was an unexpected result, given that vaccinations rates are lower among Blacks than Whites. Although pneumococcal vaccines are available free of cost to Medicare beneficiaries, and are effective in reducing the incidence and severity of PD, it has been widely recognized that vaccines are underutilized by adults especially among minority races and ethnic groups (10, 25, 26). In a national survey of people aged 65 years and older, in 2001 the average influenza and pneumococcal coverage levels reported were 66% for non-Hispanic Whites, 48% for non-Hispanic Blacks, and 54% Hispanics (26). In

Arkansas, great health racial disparities exist mainly between Black and Whites (27, 28). According to a survey by the Behavioral Risk Factor Surveillance System during 2011 to 2013, Black adults reported about 20% lower pneumococcal pneumonia vaccination prevalence than White adults in Arkansas (29). Additionally, a study on bacteremic pneumonia among adults in the US using ABCs data from 2003 to 2004 showed greater rates among Blacks than Whites in all age groups (30).

Several chronic conditions have been identified as PD risk factors, including having chronic obstructive pulmonary disease (COPD), asthma, coronary heart disease (CHD), diabetes mellitus and being a smoker (31, 32, 33). In Arkansas Blacks experience higher CHD (34), diabetes prevalence, and diabetes mortality than Whites (35); however, deaths due to chronic lower respiratory disease, pneumonia and influenza are disproportionately higher among Whites than in Blacks (12, 28). An adult tobacco use survey from 2002 to 2008 found that even though similar prevalence of smokers were found among Blacks and Whites, Whites consumed a greater average number of cigarettes per day (36). The different distribution of PD risk factors such as COPD and smoking behavior in these two racial groups may be maintaining lower PP rates among Blacks than Whites in Arkansas.

Adults in both age groups residing in rural populations experienced significantly higher PP hospitalization rates than urban populations. This is likely driven by disparities in health-care delivery, especially vaccinations in rural areas have been well documented (37). Arkansas has one of the highest proportion of rural populations in the US, and people in these areas experience serious barriers to health-care as a result of shortage of personal health services, primary care doctors and hospitals (12).

It is important to note that the decline for adults 65 years and older in rural populations

was found to be significantly higher than that in urban populations from 2010 to 2013. This rapid decline in rural regions may explain that by 2013 adults 65 years and older in urban and rural regions experience similar hospitalization rates. A study on adult vaccinations in rural versus urban counties in the US based on a 2005 Behavioral Risk Factor Surveillance system survey found that adults 65 years and older in rural areas had greater odds of having received an influenza vaccination than urban adults. While for pneumococcal vaccinations, older adults in urban and rural counties were equally likely to have been vaccinated (38). Greater protection from influenza infections may be driving the decline in rural compared to urban populations.

This study has a few limitations. First, our sample only includes hospitalized adult PP cases. Thus, the results only pertain to the most serious cases that require hospitalization. A complete assessment of impact of vaccinations in this population should include all adult cases. Second, some populations may be missing in our sample. It is possible that many cases in these counties may have been overlooked. Another population that may have been missed are Arkansas residents living close to state borders who may have attended hospitals in cities located in neighboring states. Information on these cases will not be reported in the Arkansas state HDD. Veterans who attend VA hospitals in Arkansas were also missed but they are likely to be a small number of cases, since Veterans are more likely to attend hospitals in their community than the VA hospital. Third, our case designation is based on ICD-9-CM codes, thus we are unable to validate the PP cases via laboratory test results. However, since it is known that most pneumonia cases are caused by *Streptococcus pneumoniae* (2, 23), validation may not be a big concern.

We described the trend and burden of adult hospitalized PP in different sub-population groups in a large sample in Arkansas. We observed that those 65 years and older experienced higher rates of hospitalization, but experienced greater annual percent declines in PP

hospitalization rates than adults 18 to 64 years. No sex disparities were identified. On the other hand, Whites experienced higher rates and lower annual percent declines than Blacks and rural experienced higher rates than urban populations. With a rapidly aging population (12) and increasing rates of chronic illnesses in Arkansas (28, 33, 34), the burden of PD is likely to rise; thus, this study can help identify sub-populations at high risk and inform future immunization campaigns.

2.5. Figures and Tables

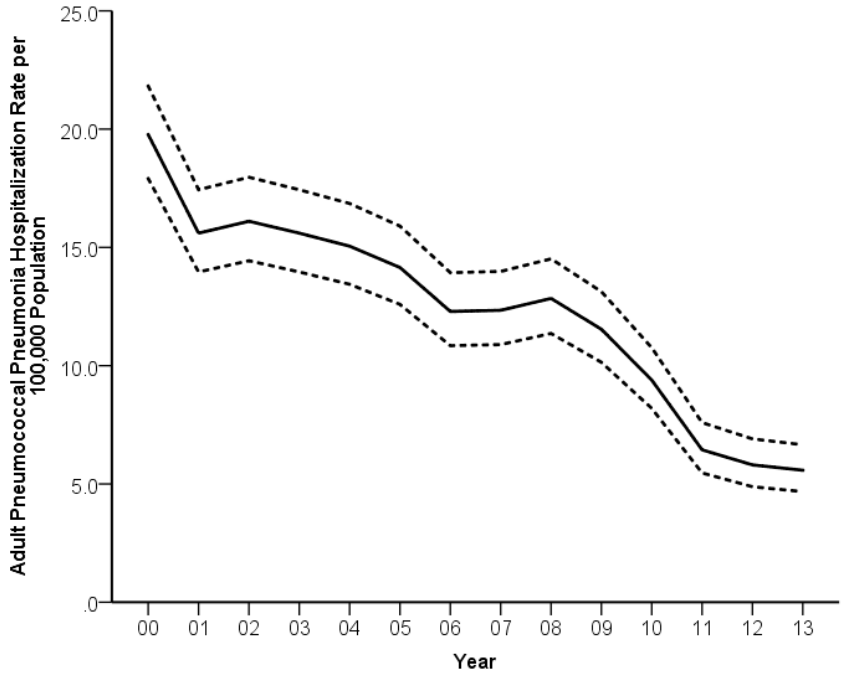

Figure 2.1. Adult PP annual hospitalization rates in Arkansas from 2000 to 2013 (solid line) and confidence intervals based on the NB distribution (dotted lines).

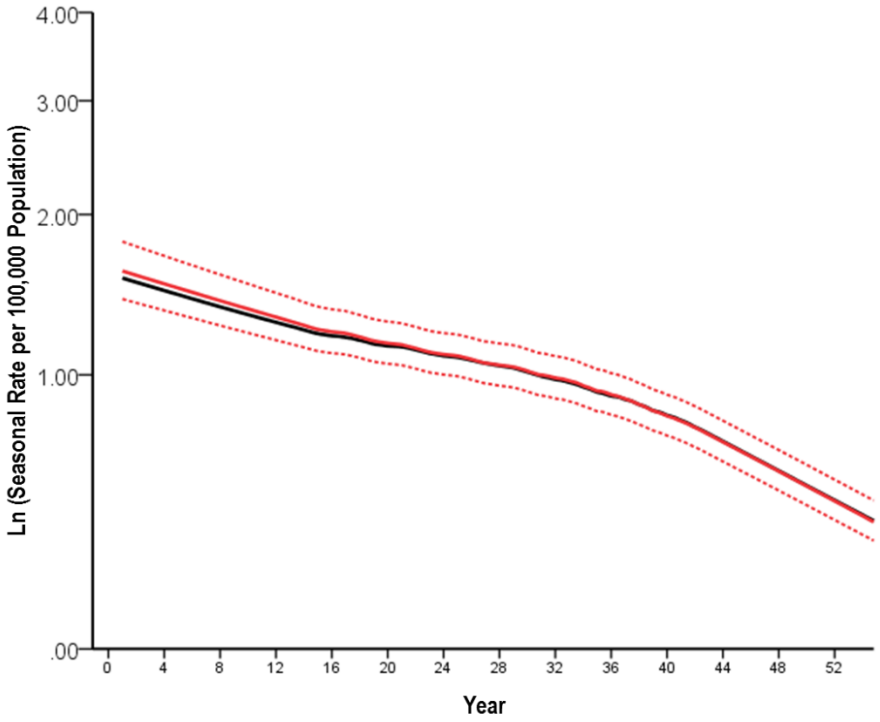

Figure 2.2. Loess plot fitted to the log of observed seasonal adult PP hospitalization rates (black line) and the log of the seasonal rates from the segmented NB model (red lines). Dotted lines are confidence intervals.

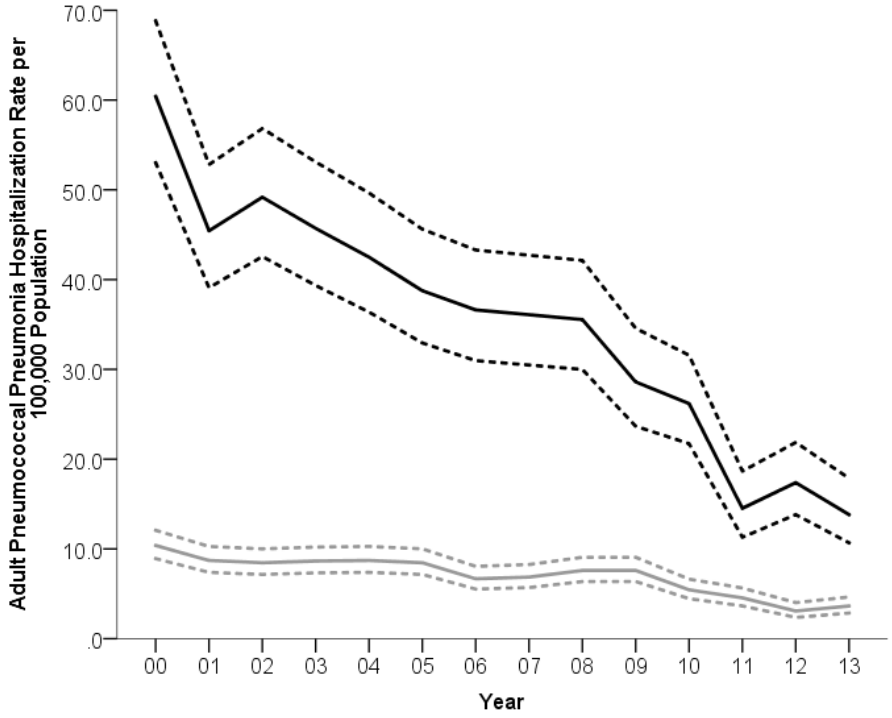

Figure 2.3. PP annual hospitalization rates in Arkansas from 2000 to 2013 for adults 18 to 64 year (grey line) and 65 years and older (black lines) with confidence intervals (dotted lines) based on NB distribution.

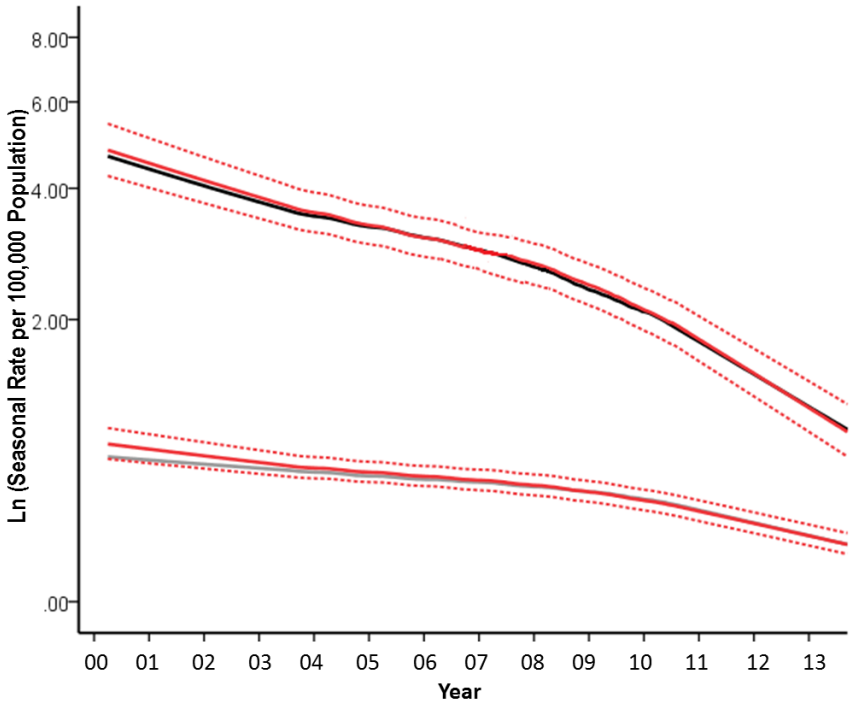

Figure 2.4. Loess plot fitted to the log of observed PP seasonal hospitalization rates for adults 18 to 64 years (grey line) and adults 65 years and older (black line) and the log of seasonal rates from the segmented NB model (red lines). Dotted lines are confidence intervals

Table 2.1. Distribution of demographic characteristics among 3,484 cases of adult hospitalized PP cases during 2000 to 2013 reported in Arkansas HDD.

		Number of Cases	Percent
Total		3,484	100.0
Sex	Male	1,710	49.1
	Female	1,774	50.9
Age	18 to 64 years	1,623	46.6
	65 years and older	1,861	53.4
Race	White / Caucasian	2,783	79.9
	Black / African-American	338	9.7
	Other	57	1.6
	Unknown	306	8.8
Residence	Urban	1,731	49.7
	Rural	1,752	50.3

Table 2.2. Adult PP hospitalization rate ratio among subpopulation groups in Arkansas stratified by age group 18 to 64 years and 65 years and older, during year a) 2000 and b) 2013 based on segmented NB regression models with time and subpopulation group interactions.

		18 to 64 years		65 years and older	
Subpopulation		Incidence Rate Ratio at year 2000 (95% CI)	P-value	Incidence Rate Ratio at year 2000 (95% CI)	P-value
a)			**2000**		
Sex	Male	1		1	
	Female	1.08 (0.86, 1.35)	0.521	0.75 (0.64, 0.90)	0.001
Race*	Whites	1		1	
	Blacks	1.01 (0.79, 1.51)	0.571	0.645 (0.41, 1.01)	0.056
Residence	Urban	1		1	
	Rural	1.11 (0.87, 1.43)	0.400	1.26 (1.06, 1.50)	0.009
b)			**2013**		
Sex	Male	1		1	
	Female	0.77 (0.49, 1.20)	0.247	1.01 (0.66, 1.54)	0.964
Race	Whites	1		1	
	Blacks	0.41 (0.20, 0.84)	0.014	0.30 (0.09, 0.93)	0.038
Residence	Urban	1		1	
	Rural	1.57 (0.97, 2.52)	0.064	0.81 (0.53, 1.24)	0.337

* First year of observation for race analysis was 2003.

Table 2.3. Adult PP hospitalization rate annual percent decline among subpopulation groups stratified by age groups 18 to 64 years and 65 years and older during years a) 2000 to 2009 and b) 2010 to 2013 based on segmented NB regression models with time interactions testing the effects of time, gender, race and area of residence and time and subpopulation group interactions.

		18 to 64 years		65 years and older	
Subpopulation		Average Percent Change (95% CI)	P-value	Average Percent Change (95% CI)	P-value
a)		**2000 to 2009**			
Sex	Male	-2.67 (-5.45, 0.00)		-6.57 (-8.79, -4.30)	
	Female	-4.67 (-7.32, -1.98)	0.293	-5.82 (-8.06, -3.93)	0.640
Race*	Whites	-3.53 (-6.20, -0.40)		-5.45 (-8.06, -2.37)	
	Blacks	-9.88 (-15.80, -3.15)	0.076	-10.24 (-19.10, -0.40)	0.316
Residence	Urban	-4.69 (-7.32, -1.98)		-6.20 (-8.42, -3.92)	
	Rural	-3.53 (-6.20, -0.40)	0.543	-6.20 (-8.06, -4.30)	0.965
b)		**2010 to 2013**			
Sex	Male	-15.12 (-21.96, -7.32)		-23.81 (-29.95, -17.14)	
	Female	-20.07 (-27.09, -12.36)	0.291	-18.78 (-24.72, -12.01)	0.222
Race	Whites	-15.12 (-20.70, -9.15)		-21.02 (-25.92, -15.46)	
	Blacks	-30.23 (-41.49, -16.81)	0.036	-31.87 (-48.93, -9.52)	0.303
Residence	Urban	-19.75 (-26.80, -12.01)		-16.81 (-22.89, -9.88)	
	Rural	-13.76 (-21.65, -5.07)	0.239	-25.62 (-31.61, -19.10)	0.038

* Race analysis limited to years 2003 to 2009.

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Chapter 3

Adult Invasive Pneumococcal Disease Trends in Arkansas, 2000 to 2013

3.1. Introduction

Streptococcus pneumoniae may cause mild and severe infections. Among the most severe types is IPD, which is an infection of a sterile body fluid such as blood or cerebrospinal fluid and manifests at meningitis, sepsis or bacteremia (1). The bacterium's capsular polysaccharide appears to be the most important factor in determining whether the bacterium is able to cause IPD. (2). More than 50,000 cases of pneumococcal bacteremia and about 6,000 cases of pneumococcal meningitis occur every year in the US. Pneumococcal bacteremia or meningitis occurs in 25% to 30% of cases with PP (3). Those most affected are children below the age of two and adults 65 years and older. Among adults, increasing age and underlying comorbidities such as diabetes and heart disease, or who smoke significantly increases risk for IPD (4). Case fatality rates among adults are about 20%, but can be as high as 60% among the elderly (3).

Currently, two types of pneumococcal vaccines are available against IPD – PPSV23 and the conjugate vaccines (PCV7 and PCV13). A recent meta-analysis revealed that PPSV23 is effective at protecting from IPD. However results were inconclusive in regards to pneumonia (5). A past study also showed PPSV23 is more effective in immunocompetent adults than immunocompromised adults (6), and it is not effective in infants and toddlers because they do not respond well to the t-cell-dependent antigens from polysaccharide vaccines (7). Despite PPS23 vaccine being recommended since 1988 for all adults 65 years and older, its uptake has

been low, especially among ethnic and racial minority populations such as Blacks and Latinos (8). The conjugate vaccines also contain polysaccharides but these are covalently linked to proteins, thus are able to induce T-cell-dependent responses in young children. The introduction of conjugate vaccines among children, PCV7 in 2000 and PCV13 in 2010 has resulted in declines in vaccine-type invasive infections in older adults as a result of indirect "herd" effects (9,10). Another outcome from the introduction of conjugate vaccines was the rise in PD infections caused by serotypes not included in the vaccines among all age groups (10).

Arkansas is nationally ranked very low in terms of overall health as a result of high rates of chronic diseases, poverty and large proportions of people living in rural areas with low or no access to health-care services. Among the top ten leading causes of death in the state of Arkansas are blood infections such as bacteremia (11). Based on this context this study examined adult IPD trends in Arkansas to understand the impact of vaccine interventions and identify over-burdened sub-populations in order to inform immunization policy in Arkansas.

3.2. Methods

3.2.1. Study Population and Data Sources

The study sample was composed of all adults (18 years and older) hospitalized for IPD in Arkansas from January 1, 2000 to December 31, 2013. The study subjects were extracted from the Arkansas HDD using ICD-9-CM codes indicative of IPD. A patient was included based on the following inclusion criteria: 1) a first listed diagnosis code for pneumococcal meningitis, pneumococcal bacteremia or septicemia, or pneumococcal peritonitis 2) a first listed diagnosis code for unspecified meningitis, septicemia, bacteremia or another type of invasive infection (peritonitis, osteomyelitis, pyogenic arthritis) and a second listed code indicating *S. pneumoniae* infection (Table 3.1). Cases extracted from HDD included all adult IPD patients that presented to

a hospital within the state except for cases that presented to the two VA hospitals in Arkansas because HDD does not record VA hospital visits.

De-identified patient demographics (sex, age, race and geographic residence) were also extracted. Urban or rural geographic residence classifications were derived from patient's zip code and by using methods previously described, based on the Census Bureau MSAs defined by the Office of Management and Budget (12, 13). The study was approved by the Institutional Review Board for Health Science and Behavior Science at the University of Michigan and the Arkansas Department of Health's Science Advisor Committee.

3.2.2. Incidence Rate Calculations

In order to understand overall and sub-population specific trends, IPD annual hospitalization rates for the total population and subpopulations were calculated using the population estimates from the 2000 and 2010 U.S. census (14). The year 2000 census population estimate were used to calculate annual rates from 2000 to 2009 and the 2010 estimates were used for the 2010 to 2013 annual rate calculations. Due to the strong seasonal component impacting pneumococcal disease in which incidence peaks in the winter months (15), seasonal incidence trends were explored. Seasonal incidence rates were calculated by dividing the number of cases per season (Winter- December to February; Spring- March to May; Summer- June to August; and Fall- October to December) by the total Arkansas population times four. Confidence intervals for annual rates were calculated by modeling the observed rates using a Poisson regression model with time as categorical variable.

3.2.3. Model Building

To understand the annual percent change over the 14 years of observations, we modeled the overall and subpopulation seasonal rates using Poisson regression models with an offset for

person-time using generalized linear models. We utilized segmented regression by including a knot variable in the model at the time point (year 2010) in which the direction of the trends changed in order to adjust for the time effect. Only knots that were shown to be significant were retained in the models. The only significant knot identified was at year 2010.

Since IPD risk is strongly correlated with age and the current adult pneumococcal vaccine recommendation targets individuals 65 years and older (4), all analyses were age stratified for adults 18 to 64 years and adults 65 years and older. To assess whether there was any difference in the annual percent change in adult IPD hospitalization rates over the time between different subpopulation groups including sex (males and female), race (Whites and Blacks) and residence (urban and rural) we made use of univariate segmented Poisson regression with time interactions. Analysis of subpopulations were performed one at a time. For each analysis the model included; seasons, one demographic variable, the segmented time variables and the interactions between time segments and the demographic variable. If a regression coefficient of the interaction terms is significantly different from zero, it indicates that the demographic variable is significantly associated with a percent decline in the rate of IPD. All subpopulation comparisons were also age stratified. Annual percent change were calculated based on the seasonal change estimated by the models. Race analyses was limited to years 2003 to 2013 due to large proportions of cases with missing race information during years 2000 to 2002. All statistical analyses were performed in IBM Statistics SPSS for Windows version 22 (IBM Corp., Armonk, N.Y., USA) (16). In all the analyses, p-values <0.05 were considered to be statistically significant.

3.3. Results

3.3.1. Characteristics of the Study Population

A total of 2,175 adult IPD cases were extracted from HDD from January 1, 2000 to December 31, 2013, and 97.6% (2,121) of cases had a first listed diagnosis code indicative of a pneumococcal invasive infection. Over 90% (2,009) of cases reported with bacteremia or sepsis and 6.7% (47) of cases presented with meningitis. The remaining cases presented with other types of invasive pneumococcal infections including pyogenic arthritis, peritonitis, osteomyelitis and epiglottitis. There were about equal proportion of cases 18 to 64 years and 65 years and older. There were slightly more females than males and more urban than rural cases. The majority of cases were White (81.2%) and 11.7% were Black. (Table 3.2).

3.3.2. Adult IPD Hospitalization Trends

Over the 14 years observation period, the average annual adult IPD hospitalization rate was 7.66 per 100,000 population (95% CI: 6.07, 9.50). The annual trend from 2000 to 2013 displays an oscillating pattern (Figure 3.1). The overall adult IPD trend showed a significant rise in rates from years 2000 to 2009 of 3.66% per year (95% CI: 2.02, 4.92) ($p<0.001$) and a significant decline of 11.31% per year (95% CI: 15.46, 6.57) ($p<0.001$) from years 2010 to 2013 (Figure 3.2). The difference in annual percent IPD rate change between the first segment (2000 to 2009) and the second segment (2010 to 2013) was found to be significant ($p<0.001$) (Figure 3.2).

3.3.3. Age Stratified (18 to 64 years and 65 years and older) Adult IPD Hospitalization Trends

The average annual IPD hospitalization rate over the 14 years among those 18 to 64 years was 4.72 per 100,000 population (95% CI: 3.37, 6.37), while for those 65 years and older it was 20.36 per 100,000 population (95% CI: 14.52, 27.48) (Figure 3.3). Adult IPD hospitalization rates among those 65 years and older were consistently higher than rates among adults 18 to 64 years. In 2000, adults 65 years and older experience 5.16 (95% CI: 4.27, 6.24) times higher rates

than those 18 to 64 years (Figure 3.4). During 2000 to 2009, the trend for both age groups shows a gradual increment in IPD rates of 4.92% per year (95% CI: 2.84, 7.04) ($p<0.001$) for adults 18 to 64 years and 2.43% (0.40, 4.08) ($p=0.028$) for adults 65 years and older (Figure 3.4). The estimated annual percent change for the younger age group was found to be higher than the change for the older age group ($p=0.040$).

During 2010 to 2013 both age groups demonstrated a significant decline of 12.36% per year (95% CI: 17.80, 6.20) ($p<0.001$) for those 18 to 64 years and 11.66% per year (17.47, 5.45) ($p<0.001$) (Figure 3.4). The estimated annual percent decline was not significantly different between age groups ($p=0.886$). In year 2013 adults 65 years and older experienced 4.41 times (95% CI: 3.28, 5.91) higher rates than those 18 to 64 years (Figure 3.4).

3.3.4. Male and Female Adult IPD Hospitalization Trends

Throughout the observation period, males and females 18 to 64 years old did not experience significantly different IPD hospitalization rates (Tables 3.3a and 3.3b). Among adults 18 to 64 years, male and female trends followed the same trajectory: during the first segment (2000 to 2009) IPD trend significantly increased and in the second segment (2010 to 2013) they significantly decreased (Tables 3.4a and 3.4b).

As with the younger age group, males and females 65 years and older experienced similar IPD hospitalization rates throughout the study period (Tables 3.3a and 3.3b). In the first segment (2000 to 2009), males showed a significant increment in annual IPD rates of 3.66% per year (95% CI: 0.40, 6.61), while the change among females was not significant (0.40% per year 95% CI: -2.37, 2.84) (Table 3.4a). However, the difference between male and females was not significant ($p=0.078$). In the second segment (2010 to 2013), females demonstrated a greater decline in IPD annual rates than males (11.31% vs. 4.30% per year), however the difference was

not significant (p=0.205) (Table 3.4b).

3.3.5. Black and White Adult IPD Hospitalization Trends

To understand the impact of racial health disparities in Arkansas among adults with IPD, we compared trends between the two major racial groups in Arkansas, Blacks and Whites (11). Among those 18 to 64 years old, Blacks initially experienced 1.57 (95% CI: 1.08, 2.27) times higher rates than Whites (Table 3.3a). During 2003 to 2009, Whites demonstrated significant increment in annual IPD rates of 5.33% per year (95% CI: 1.61, 9.20), while for Blacks no significant change was identified (Table 3.4a). In the second segment (2010 to 2013) both Blacks and Whites trend exhibited a significant decline. However, the decline among Blacks was significantly greater than that among whites (35.60% vs. 8.79% per year) (p=0.002) (Table 3.4b). Thus, in 2013 Whites experienced 69% higher rates than Blacks (p=0.003) (Table 3.3b).

Among those 65 years and older, the IPD rates for Blacks and Whites were not significantly different throughout the study period (Tables 3.3a and 3b). During 2003 to 2009 we identified non-significant changes in Black and White IPD trends (Table 4a). While during the 2010 to 2013 segment, we found a significant decline among Whites of 10.95% per year and no significant change was among Blacks (Table 4b). These differing trends were found to be marginally significant (p=0.060) (Table 4b).

3.3.6. Urban and Rural Adult IPD Hospitalization Trends

Rural and urban IPD hospitalization trends were compared because the majority of the Arkansas population is considered rural where access to health-care services is not comparable to those in urban areas (11). In 2000, among those 18 to 64 years, rural populations experienced 30% (95% CI: 3.0, 49.0) lower rates than urban populations (p=0.033) (Table 3.3a). During 2000 to 2009, rural IPD hospitalization rates showed a significantly higher annual rate increment than

urban populations (8.33% vs. 3.66% per year) (p=0.042) (Table 3.4a). In the second segment (2010 to 2013), urban populations demonstrated a greater annual decline in rates than rural populations (18.50% vs. 8.10% per year), however the difference was not significant (p=0.090) (Table 3.4b). By the end of the study period, rural populations experienced higher rates than urban, however the difference was not significant (p=0.155) (Table 3.3b).

Among those 65 years and older, urban and rural populations experienced similar IPD rates throughout the study period (Table 3.3a and 3b). During 2000 to 2009, urban populations experienced a significant increment in percent IPD rates of 3.25% per year (95% CI: 0.40, 6.61) while at the same time rural populations showed a non-significant decline (Table 3.4a). This difference in percent annual change in IPD rate between urban and rural was not significantly different (p=0.094) (Table 3.3a). During 2010 to 2013 the rate for urban populations declined significantly faster than rural populations (16.14% vs. 1.61%) (p=0.014) (Table 3.4b). The percent annual change for rural populations from 2010 to 2013 was not significant (p=0.777) (Table 3.4b).

3.4. Discussion

In order to understand the impact of childhood pneumococcal vaccinations on adult IPD trends in Arkansas, this study made use of 2,175 IPD cases 18 years and older identified in HDD from 2000 to 2013. The overall trend demonstrated a significant percent annual rate increment from 2000 to 2009 and a decline from 2010 to 2013. Most subpopulation groups except for Blacks in the 18 to 64 years age group showed a rate increment in the first segment. For adults 65 years and older the annual percent rate increment was smaller than the younger age group. In the second segment from 2010 to 2013, most groups exhibited a significant annual rate decline or no change except adults 65 years and older in rural populations.

Many studies (17, 18, 19) reported steep declines in adult IPD rates in US populations shortly after introduction of PCV7 in children in the year 2000. Notably, a study on 8 metropolitan areas in the US identified significant declines in annual percent IPD incidence ranging from 17% to 35% per year among adults 50 years and older in different age categories when comparing rates from 1998 to 1999 and 2000 to 2003 (17). In this study, a small, non-significant decline was observed from 2000 to 2003 (Figure 3.2), which may be attributed to the indirect effects of the introduction of PCV7 in 2000. When considering the entire trend from 2000 to 2009, a significant increment in percent annual adult IPD rates was identified. When comparing trends for adults 18 to 64 years and 65 years and older, we find that older adults experienced a significantly lower IPD rate increment from 2000 to 2009 than younger adults in Arkansas (Table 3.4). A similar finding was identified in the study mentioned earlier in which younger adults (50 to 64 years) experienced the lowest decline of 17% while adults 65 years and older experienced greater declines between 28% and 35% (17). This finding may reflect the positive impact of the PPSV23 vaccine recommendation on adults 65 years and older.

Although adults 65 years and older experience about five times higher IPD rates than younger adults (18 to 64 years), the trend for adults 65 years and older displayed a non-significant decline from 2000 to 2003, after which hospitalization rates begin to rise (Figure 3.4). This dip in IPD rates right after the introduction of PCV7 is not observed in the adults 18 to 64 years trend line (Figure 3.4). These results are similar to a study on IPD in adults 50 years and older in Olmstead Country, Minnesota from 1999 to 2007 which found that after the PCV7 vaccine introduction, IPD rates declined non-significantly from 2000 to 2003. However, from 2004 to 2007 they found IPD incidence rates increased by 45% per year, as a result of a 72% rise in infections due to serotypes that were not included in PCV7 (18). Another study among

Alaskan Natives 45 years and older also attributed the 43% increments in IPD rates post-PCV7 as a result of a 121% rise in infections due to non-PCV7 serotypes (19). Unfortunately, we do not have serotype information in this study, but it is possible that the increase in non-PCV7 serotype disease has offset the indirect effect of decreasing infections by PCV7 serotypes. It would be of interest to compare serotype distribution of adult IPD cases Arkansas before and after vaccine interventions to fully understand the impact of pneumococcal childhood vaccinations among adults in this population.

Several studies have shown that males experienced greater IPD incidence rates than females (17, 20). A study in Atlanta, Georgia among individuals of all ages from 1997 to 2004 showed that males had a 35% (95% CI: 26.0-44.0) higher risk of IPD than females (20). In another study on pneumococcal disease mortality post-PCV7 (2001 to 2004) in the US, men were 32% (95% CI: 26.0, 39.0) more likely to die than females (21). In this study, rates among males and females did not significant differ and both experienced similar trend trajectories. Similar to these results, the study mentioned earlier by Lexau et al. (17) on eight metropolitan areas in the US identified similar IPD rate trends among males and female: 27% decline in rates post-PCV7.

Since 2000, the Active Bacterial Core Surveillance (ABCs), which surveils a population of over 30 million people of all ages in the US, has consistently reported higher IPD rates among Blacks and the lowest rates among Whites (22). However, since 2000 the rate among Blacks has been decreasing more rapidly than rates among Whites (22). A similar situation is mirrored in these results. During 2003 to 2009 Blacks in both age groups showed no significant changes in annual rates, while their White counterparts display annual rate increments. Even though change among Blacks are not significant, it is important to note that Blacks made up only 12% of the

sample size. Thus the race analysis may not have enough power to detect significant trend changes among Blacks. In the 2010 to 2013 segment, we find that the annual decline in IPD rates among Blacks 18 to 64 years is significantly greater than that among Whites. Among those 65 years and older, Blacks demonstrate a non-significant rise in trends. This unexpected trend may be the result of a small sample size of only 74 cases of Blacks 65 years and older.

Given the limited access to health care services in rural areas in Arkansas (11, 23), we expected to find a greater burden of disease among rural than urban populations. Among both age groups, we find that, by the end of the study period, higher IPD rates were observed among rural populations. Additionally, we found steep and significant declines in annual IPD rates among urban populations post-PCV13, while rural populations did not show significant changes during this time. Differences between urban and rural adult IPD trends may suggest important disparities in access to pneumococcal vaccines may exist in Arkansas. For example the cost of vaccines for family practices where most rural children in Arkansas are vaccinated has been well documented (24). Also, the introduction of the philosophical vaccine exemption in 2003 in Arkansas resulted in more than doubling the number of granted exemptions to children in grades kinder to 12 in only two year. Many of these exempt cases were found to cluster in rural school counties, such as Dewitt (25). Recent reports have shown that the number of vaccine exemptions has continued to increase in recent years (24).

This study has several limitations. First, our sample only included hospitalized adult IPD cases and thus we may be missing cases that may have been treated at clinics. However, given that IPD is a very serious illness, it is likely that the number of IPD cases that do not present to hospitals is negligible. Another study also noted the practicality of HDD to evaluate reporting of serious diseases the require hospitalization (26). Our study sample is, however, lacking

information on VA hospital cases. Second, Arkansas is largely rural and as of 2008 there were 21 counties that do not have ready access to a hospital (23). Thus, it is possible that many cases in these counties may be have been overlooked. Third, our case designation is based on ICD-9-CM codes in HDD, thus we are unable to validate IPD cases without laboratory exam results. It is possible that IPD in HDD may be over-reported. Lastly, due to small proportion of Blacks in Arkansas (11) and the small number of Black cases in this sample severely limits the validity of the race analysis.

In conclusion, adult annual IPD rate trends in Arkansas demonstrated a slight incline in earlier years followed by a more recent marked decline. These unexpected results may suggest that the PCV7 introduction rapidly gave rise a to a serotype replacement phenomenon which increase IPD infections caused by non-vaccine serotypes. The full of impact of the PCV13 on adult IPD is still not fully known, although marked declines in rates have been observed, we do not know how long these effects will last.

3.5. Figures and Tables

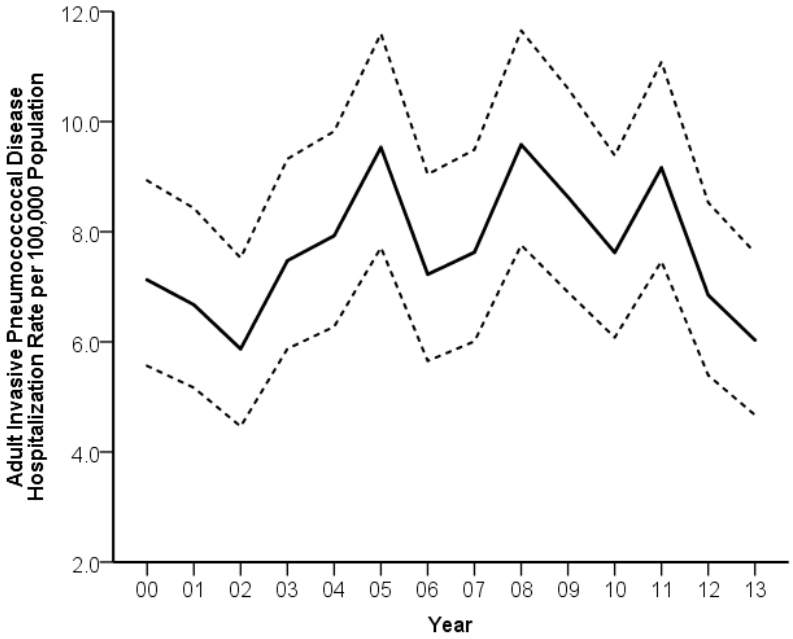

Figure 3.1. Annual adult IPD hospitalization rates per 100,000 population in Arkansas from 2000 to 2013 and confidence intervals (dotted lines) based on the Poisson distribution.

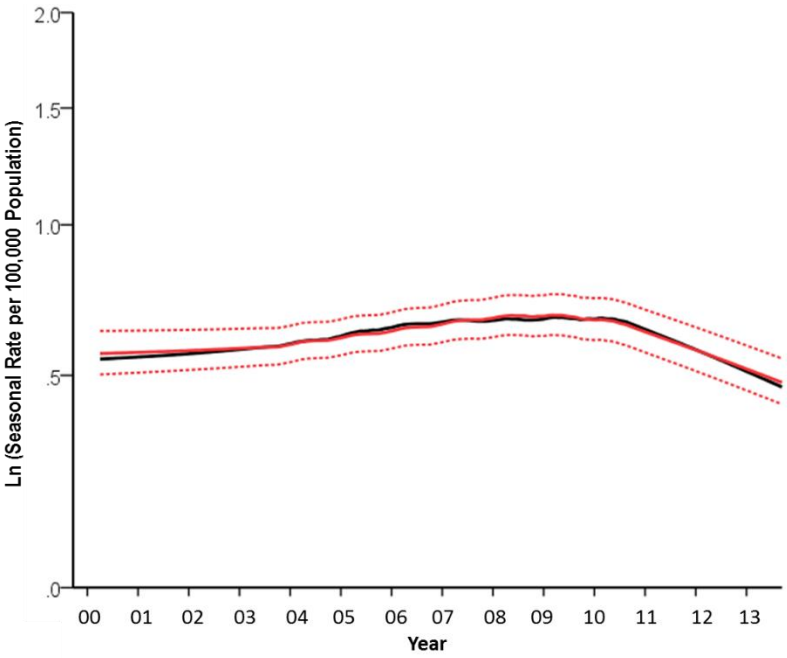

Figure 3.2. Loess plot fitted to the log of observed seasonal adult IPD rates (solid lines) from 2000 to 2013 in Arkansas and log of seasonal adult IPD rates from Poisson regression model. Dotted lines are confidence intervals.

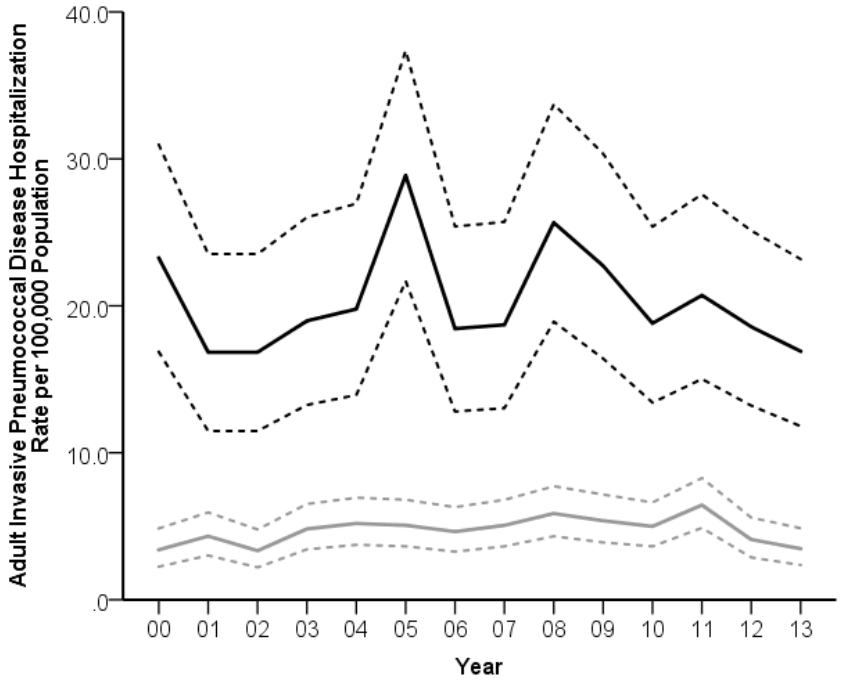

Figure 3.3. Annual adult IPD hospitalization rates per 100,000 population and confidence intervals (dotted lines) for adults 18 to 64 years old (grey lines) and 65 years and older (black line) Arkansas from 2000 to 2013 and confidence intervals based on the Poisson distribution

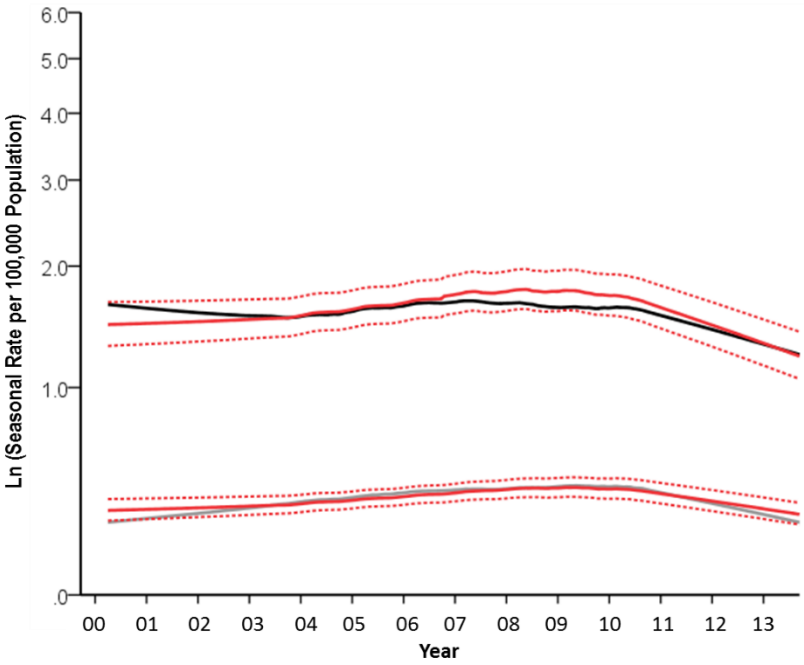

Figure 3.4. Loess plot fitted to the log of observed seasonal IPD rates for adults 18 to 64 years old (grey line) and adults 65 years and older (blacks line) in Arkansas and log of seasonal adult IPD rates from Poisson regression model. Dotted lines are confidence intervals.

Table 3.1. Primary and secondary ICD-9-CM codes used to identify invasive pneumococcal disease cases in hospital discharge data from 2000 to 2013.

Invasive Pneumococcal Disease Type	ICD-9-CM Codes	
	Primary	Secondary
Septicemia or Bacteremia	038.0	-
	038.8, 0.38.9, 785.52, 790.7, 995.91, 995.92	041.2
Meningitis	320.1	-
	320.2	-
	320.7, 320.89, 320.9, 322.0, 322.9	041.2
Other	567.1	-
	567.9, 730.20-29, 711.00-09	041.2

Table 3.2. Distribution of demographic characteristics among 2,175 adult invasive pneumococcal disease cases in Arkansas from 2000 to 2013 reported in hospital discharge data.

		Number of Cases	Percent
Total		2,175	100.0
Sex	Male	997	45.84
	Female	1,178	54.16
Age	18 to 64 years	1,086	49.93
	65 years and older	1,089	50.07
Race	White / Caucasian	1,766	81.19
	Black / African-American	258	11.86
	Other	55	2.54
	Unknown	96	4.41
Residence	Urban	1,258	57.84
	Rural	916	42.11
	Unknown	1	0.05
IPD Type	Bacteremia	2,009	92.37
	Meningitis	147	6.76
	Other	19	0.80

Table 3.3. Adult IPD incidence rate ratio among subpopulations groups based on segmented Poisson regression models with time interactions stratified by age groups 18 to 64 years and 65 years and older at the a) first (2000) and b) last (2013) year of observation.

		18 to 64 years		65 years and older	
Subpopulation		Incidence Rate Ratio at year 2000 (95% CI)	P-value	Incidence Rate Ratio at year 2000 (95% CI)	P-value
a)		**2000**			
Sex	Male	1		1	
	Female	1.03 (0.78, 1.36)	0.808	1.28 (0.97, 1.67)	0.075
Race*	Whites	1		1	
	Blacks	1.57 (1.08, 2.27)	0.017	1.07 (0.64, 1.78)	0.801
Residence	Urban	1		1	
	Rural	0.70 (0.51, 0.97)	0.033	1.04 (0.78, 1.39)	0.787
b)		**2013**			
Sex	Male	1		1	
	Female	0.83 (0.54, 1.27)	0.396	0.79 (0.53, 1.20)	0.284
Race	Whites	1		1	
	Blacks	0.31 (0.15, 0.68)	0.003	1.54 (0.78, 3.07)	0.216
Residence	Urban	1		1	
	Rural	1.41 (0.88, 2.26)	0.155	1.45 (0.92, 2.29)	0.108

*Race analysis was limited to years 2003 to 2009.

Table 3.4. Average annual percent change of adult IPD incidence rate from Poisson regression models testing the effects of time, gender, race and areas of residence and interactions of time and race, time and gender, time and residence in Arkansas a) from 2000 to 2009 and b) from 2010 to 2013.

		18 to 64 years		65 years and older	
Subpopulation		Average Percent Change (95% CI)	P-value	Average Percent Change (95% CI)	P-value
a)		**2000 to 2009**			
Sex	Male	6.18 (3.25, 9.20)		3.66 (0.40, 6.61)	
	Female	4.92 (2.02, 7.90)	0.569	0.40 (-2.37, 2.84)	0.078
Race*	Whites	5.33 (1.61, 9.20)		2.02 (-1.59, 5.76)	
	Blacks	-4.69 (-11.31, 2.02)	0.008	-5.82 (-16.14, 5.76)	0.192
Residence	Urban	3.66 (0.80, 6.61)		3.25 (0.40, 6.61)	
	Rural	8.33 (4.50, 12.30)	0.042	-0.80 (-3.92, 2.84)	0.094
b)		**2010 to 2013**			
Sex	Male	-13.06 (-21.02, -4.69)		-4.30 (-13.06, 5.34)	
	Female	-16.81 (-24.72, -8.42)	0.484	-11.31 (-19.01, -3.15)	0.205
Race	Whites	-8.79 (-15.46, -1.19)		-10.95 (-17.80, -3.53)	
	Blacks	-35.60 (-48.11, -20.07)	0.002	14.11 (-10.59, 46.23)	0.060
Residence	Urban	-18.50 (-26.22, -9.90)		-16.14 (-24.72, -6.57)	
	Rural	-8.10 (-17.80, 2.84)	0.090	1.61 (-9.15, 13.60)	0.014

*Race analysis was limited to years 2003 to 2009.

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Chapter 4

Assessment of the Functioning of the Arkansas State Adult Invasive Pneumococcal Disease Surveillance System, 2003 to 2013

4.1. Introduction

Disease surveillance systems are essential for communicable disease control and monitoring. In the US, the CSTE and the CDC, have established a list of recommended notifiable diseases and their case definitions. Each of the 50 states has mandatory regulations that require health care entities to report certain diseases at the state level (1).

Streptococcus pneumoniae invasive infections are confirmed via isolation of the bacterium from a sterile body site (blood or cerebrospinal fluid) (1). In the state of Arkansas IPD regardless of age or drug resistance status, has been a reportable condition since 2001 (2). IPD case reports from laboratories, hospitals or clinics are sent to the ADH by health care workers. The ADH then processes the information, uses it for public health purposes, and finally relays confirmed cases to the CDC using NBS at least once a week.

The NBS system has been in use in Arkansas since 2009. It was introduced to replace the NETSS in order to improve the quality and speed of transmission of communicable disease information within the state and the nation. Among its many attributes are its internet-based technology and automated laboratory results data input. Prior to NBS, health departments usually received case reports by mail or fax and then had to transcribe information unto NETSS. As a result, only about 10% to 85% of cases were reported to health authorities, depending of the

disease type (3).

Vaccine recommendations are often formulated based on research from surveillance system databases. Thus surveillance systems should be evaluated regularly to improve quality, and usefulness of information and to ensure accurate interpretation of its data. Out of the total nine attributes of surveillance systems according to CDC's Guidelines for Evaluating Public Health Surveillance Systems (4), five that were most relevant to immunization program assessment and policy decision were assessed in this study: 1) sensitivity (i.e., proportion of true cases that are detected by the surveillance system), 2) representativeness (i.e, comparison of the demographic characteristics of reported cases to cases that were not reported in the surveillance system), 3) data quality (i.e., completeness of data items in a surveillance system), 4) positive predictive value (i.e., proportion of reported cases that actually have the disease) and, 5) timeliness (i.e., interval between recognition of a notifiable disease by the physician or laboratory and receipt of the corresponding notifiable disease report by a public health agency) (4).

Invasive infections such as IPD usually require hospitalization due to their severity and the need of intravenous antibiotics to treat. The HDD is a population-based data source that has been used to identify the true number of notifiable disease cases for diseases with high hospitalization rates and simple case definitions in surveillance system assessments (5, 6, 7). In this study, we made use of Arkansas HDD as a "gold standard" of total number of cases in the state to evaluate the sensitivity of the adult IPD surveillance system in Arkansas. We also examined other surveillance system attributes: positive predictive value, timeliness, data quality and representativeness to assess the functionality of the adult IPD surveillance system in

Arkansas. We also assessed the impact of the introduction of NBS on sensitivity, data quality and representativeness.

4.2. Methods

4.2.1. Data Match and Sensitivity Analysis

Adult IPD cases (18 years and older) that presented to a hospital from year 2003 to 2013 were extracted from HDD using a first listed ICD-9-CM code indicative of IPD or a first listed code for non-specific invasive infection and a second listed code indicating *S. pneumoniae* infection (Table 4.1). HDD was used as a "gold standard" collection of cases since most IPD cases are likely to be hospitalized and thus recorded in this database. Cases in the surveillance system were then matched to HDD cases using full name, date of birth, first 3 digits of the address and zip code at the ADH. During year 2003 to 2008 cases were matched to the NETSS system while during year 2009 to 2013 the NBS was used. Annual sensitivity was calculated as the total number of matched surveillance system cases divided by the total number of cases reported in HDD for that year. Asymptotic confidence intervals were calculated as previously described (8). Simple linear regression was used to understand the direction of the trend and the annual percent change in sensitivity over time.

4.2.2. Representativeness

To understand if cases captured by the surveillance system had similar demographic characteristics as cases that were not captured, we compared the age, gender (male and female) and race (Whites and Blacks) distribution of the 510 cases in the surveillance system matched to HDD cases and the remaining 1,300 unmatched cases in HDD during 2003 to 2013. Chi-square tests of proportions were used to compare the proportions of cases in each sex and race group in HDD and the surveillance system (NETSS or NBS). For age categories we used t-tests to

compare matched and unmatched proportions of cases within age category.

4.2.3. Data Quality

Data quality was assessed by calculating the percentage of matched cases with missing key demographic variables including age, sex, race and ethnicity in NETSS and NBS. Chi-square test of proportions or fishers exact tests was used to determine the difference in the proportion of missing variables in each system.

4.2.4. Positive Predictive Value

Positive predictive value was calculated by determining the proportion of matched cases with a confirmed lab test divided by the total matched cases identified in the surveillance system.

4.2.5. Timeliness

Timeliness of the surveillance system was assessed by considering matched cases only in two ways: 1) calculating the median time between admission to the hospital and the time the report was recorded in the surveillance system. Medians were used to measure central tendency due to the skewness of the data. The necessary variables to make this calculation (investigation start date and investigation close date) where only available for cases reported from 2009 to 2013.

4.3. Results

4.3.1. Sensitivity

Out of the total 1,810 adult IPD records found in HDD from 2003 to 2013, only 510 were matched to a record in the surveillance system. The average annual sensitivity of the surveillance system 2003 to 2013 was low (28.18% [95% CI: 26.11, 30.31]). However, as shown in Figure 4.1, sensitivity has significantly increased every year at a rate of 1.92% per year (95% CI: 0.91, 2.92; p=0.002) from 2003 to 2013. Although the annual increment in sensitivity after the

implementation of NBS (2009 to 2013) is greater (2.70% per year 95% CI: -0.31, 5.71) than that during 2003 to 2008 (1.48% per year 95% CI: -0.45, 3.41), this difference is not statistically significant (p=0.540). Sensitivity for the entire study period was found to be low.

4.3.2. Representativeness

The proportions of matched and unmatched cases in each age, gender and racial group were not statistically significant during 2003 to 2008. Similar results were found in NBS (2009 to 2013), except that the proportion of cases 65 years and older is greater among unmatched than matched cases (51.19% vs 43.06%) and this difference is significant (p=0.023) (Table 3).

4.3.3. Data Quality

Data quality was 99.8% complete for the main demographic variables age and sex, however race and ethnicity was missing in 20% (183/229) of cases in NETSS (Table 4.2). In the more recent NBS, we find that the proportion of cases with missing race and ethnicity information was 27% (76/281); a significant improvement over the earlier NETSS years (2003 to 2008) (Table 4.2).

4.3.4. Positive Predictive Value

All cases in the surveillance system that were matched to HDD cases during 2003 to 2013 had an indication of a positive blood or cerebrospinal fluid laboratory culture that confirmed the infection. Thus, positive predictive value (100%) was high.

4.3.5.. Timeliness

The median time between the date when a patient was admitted to a hospital in Arkansas as recorded in HDD and the date when the case was reported in the surveillance system was 6 days (minimum=0, Quartile 1=4, Quartile 3=11, maximum=337) for the 288 cases in HDD matched to cases in the surveillance system from 2009 to 2013.

4.4. Discussion

In this study we made use of 1,810 hospital discharge adult IPD records and 510 corresponding matches in the surveillance system to understand the functioning of the surveillance system based on the following selected attributes: sensitivity, positive predictive value, timelines, data quality and representativeness. Since, we had records from 2003 to 2013, we also evaluated the impact of the implementation of the new surveillance system software (NBS) in 2009 on some of these attributes. The major findings include low sensitivity and good timeliness, positive predictive value and representativeness. Additionally, improvements in data quality and sensitivity were identified with the introduction of NBS.

Given that the Arkansas IPD surveillance system is passive, we were expecting low sensitivity. Another study on the sensitivity of the passive Arkansas state pertussis surveillance system, which used a similar approach as this study also found low sensitivity of 55% in 2012 (9). However, low sensitivity (17%) in active systems such as the *Haemophilus influenza* invasive disease surveillance in Colorado from 2003 to 2005 have also been previously reported (6). Despite an annual sensitivity of less than 50% throughout the entire study period (2003 to 2013), we found that, over time, sensitivity had been significantly increasing by about 2% per year (Figure 4.1). By year 2013, sensitivity reached its max at 44.36% (95% CI: 35.75, 53.22). Interestingly, despite the low sensitivity, we found that cases that were captured by the surveillance were very similar to cases that were not captured in regards to age, sex and racial distribution (Table 4.3). However, the low sensitivity may reflect important knowledge gaps among health care workers of reportable diseases. Thus, it is necessary to educate health care workers.

Although the sensitivity did not significantly increase after the introduction of NBS in

2009, the estimated percent annual change was still greater than that during the earlier NETSS years (2.70% vs. 1.48% per year). This difference may still be attributed to the implementation of NBS which made case reporting easier and faster, and thus resulted in greater reporting by health agencies. A study found that after incorporating some components of NEDSS at the New Jersey Department of Health in 2002, the number of notifiable disease cases being reported more than doubled in only two years. They also found that timeliness was greatly improved from an average of 28 days to report a case to the health authorities to 3 to 4 days after the implementation of the internet-based diseases reporting system (3). Although the timeliness between NETSS and NEDSS could not be compared in this study, we found that most cases in NEDSS were being reported to the ADH and to the CDC in an acceptable time frame. Since 2010, the CSTE has required all confirmed IPD cases regardless of age or drug resistant status to be notified to the CDC (10) in standard notification time of at least 7 days (11).

We also identified improvements in the data quality of the surveillance system with the NBS update. Even though important demographic variables such as race and ethnicity were found to be less than 80% complete in NETSS (2003 to 2008), we identified a dramatic decline in records with incomplete data in the later years (2009 to 2013), once NBS was in place. These results are similar to findings in CDC studies on data completeness which found 20.6% of IPD records from 2007 to 2011 with a missing race in the public health surveillance system that collects data on nationally notifiable diseases in the US (NNDSS). It has been suggested that the automatic data entry application available in NEDSS has greatly reduced the number of missing variables (12). However, 100% completeness of demographic variables are critical to make adequate use of surveillance system data to monitor IPD trends or identify subpopulations at risk (13).

Although this assessment provides insight into some attributes of the Arkansas adult IPD surveillance system to provide accurate information to inform future immunization policies, it has limitations. First, our dataset only had surveillance system cases that were matched to HDD cases, and thus we had no information of cases in the surveillance system that are not reported in HDD. We presume this would be the minority of cases because given the severity of invasive infections symptoms, nearly all patients are expected to be treated in a hospital and thus be recorded in HDD (5, 6, 7). Another population that may be missed in the both the surveillance system and HDD are Arkansas residents admitted to hospitals in border states (e.g. Texas and Tennessee). Second, our subset of matched cases in the surveillance system is further limited because we only accounted for adult cases 18 years and older. To fully understand the completeness of the data in surveillance system all cases should be considered especially. Especially, since adults 65 years and older and children less than 2 years old experience the highest IPD rates nationwide (14). Furthermore, important differences may exist between reporting of children and adult cases which should be considered. Lastly, our sensitivity analysis is largely dependent on the quality of the matching procedure. Although, many variables (name, last name, date of birth) were used to ensure accurate matching, personal unique identifiers (i.e. social security number) could not be used due to the lack of these variables in the databases. This could have led to either over- or under-calculation of sensitivity.

In order to provide the best infectious disease epidemiological data to help inform immunization policy, local and state health departments should strive to achieve 100% sensitivity and data completion. Although the Arkansas adult IPD surveillance system appears to be improving in its efforts to capture all cases with all their corresponding information, there is much room for improvement. Further, research is necessary to understand the barriers to

complete and accurate reporting of adult IPD in the state of Arkansas. Of interest would be to determine if underreporting of adult IPD cases was limited to specific health-care facilities and then proceed to remind them of reporting requirements.

4.5. Figures and Tables

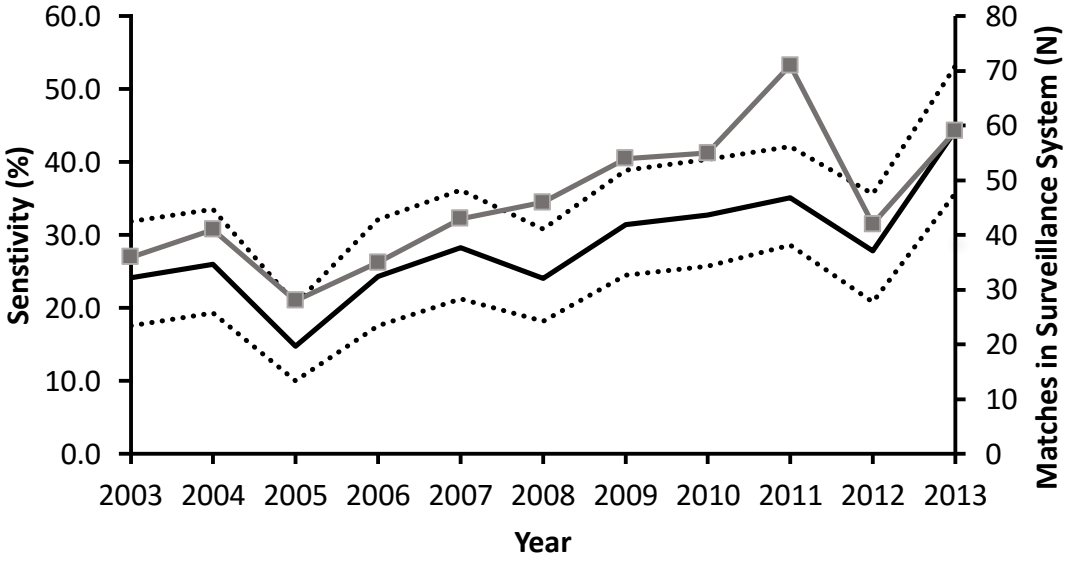

Figure 4.1. Percent sensitivity of the Arkansas adult IPD surveillance system per year (solid black line) and confidence intervals (dotted black lines) and the number of surveillance system cases matched to HDD cases (grey square line) from 2003 to 2013.

Table 4.1. Primary and secondary ICD-9-CM codes used to identify invasive pneumococcal disease cases in hospital discharge data.

Invasive Pneumococcal Disease Type	ICD-9-CM Codes	
	Primary	Secondary
Septicemia or Bacteremia	038.0	-
	038.8, 0.38.9, 785.52, 790.7, 995.91, 995.92	041.2
Meningitis	320.1	-
	320.2	-
	320.7, 320.89, 320.9, 322.0, 322.9	041.2
Other	567.1	-
	567.9, 730.20-29, 711.00-09	041.2

Table 4.2. Number and percent of adult IPD cases in the surveillance system matched to HDD with missing key demographic variables among 229 matches in NETSS (2004 to 2009) 281 matches in NEDSS (2009 to 2013) and the difference in proportion.

Demographic Variable	NETSS 2003-2009 (%)	NBS 2009-2013 (%)	P-value*
Age	0 (0.00)	1 (0.35)	1.000
Sex	0 (0.00)	0 (0.00)	1.000
Race	75 (32.75)	60 (21.35)	0.005
Ethnicity	108 (47.16)	16 (5.69)	<0.001

* Chi-square test for proportions

Table 4.3. Demographic characteristics of matched cases in NETSS and NEDSS and cases reported in HDD only for the periods 2003 to 2008 and 2009 to 2013.

		2003-2008		2009-2013	
Demographics		NETSS (%) N=229	HDD Only (%) N=755	NBS (%) N=281	HDD Only (%) N=545
Age	18-34y	14 (6.11)	47 (6.22)	18 (6.42)	29 (5.32)
	35-49y	44 (19.21)	127 (16.82)	45 (16.00)	81 (14.86)
	50-64y	63 (27.51)	201 (26.62)	97 (34.52)	156 (28.62)
	≥65y	108 (47.16)	380 (50.33)	121 (43.06)*	279 (51.19)*
Sex	Male	108 (47.16)	343 (45.43)	132 (46.97)	260 (47.71)
	Female	121 (52.84)	412 (54.57)	149 (53.02)	285 (52.29)
Race	White	195 (88.24)	644 (86.55)	238 (89.14)	473 (89.24)
	Black	26 (11.76)	100 (13.45)	29 (10.86)	57 (10.76)

* Two sample Z-test to compare proportions p-value is 0.0296

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Chapter 5

Conclusion

5.1. Summary of Major Findings

PD continue to be a major public health burden worldwide, despite available vaccines to prevent them. About 400,000 hospitalizations from PP occur in the US with a case fatality rate of 5 to 7% which significantly increases in elderly patients. IPD manifests as pneumococcal bacteremia and pneumococcal meningitis and represents a lower number of annual cases of about 20,000 per year but with much higher case fatality rates of up to 20% among adults. Among adults aging and the presence of chronic medical conditions, such as hematologic cancer, chronic heart disease, and pulmonary disease and smoking behavior can significantly increase risk for PD (1).

This dissertation made use of 14 years of data and over 5,000 adult PD cases in HDD to understand the changing epidemiology and trends of adult PD in Arkansas to inform future vaccination campaigns. Chapter two and three of this dissertation evaluates trends of the two major clinical presentations of pneumococcal diseases 1) PP and 2) IPD among adults (18 years and older) in the state of Arkansas from 2000 to 2013 in light of the introduction of children conjugate pneumococcal vaccines in 2000 (PCV7) and in 2010 (PCV13) in the US. Chapter four assesses the completion of the adult IPD records found in the surveillance system as a means to evaluate the usefulness and accuracy of the public health information it provides to guide immunization policies.

Adult PP trends demonstrate a steady and consistent decline during the entire observation period. This trends was also reflected among all subpopulation groups (adults 18 to 64 years, 65 years and older, male, females, Whites, Black, urban and rural populations) evaluated. Furthermore the decline begins to become more pronounced a shortly before the the national licensure of PCV13 in 2010. This decline was attributed to changes in Arkansas immunization policy to vaccinate all children who attended day care with PCV7 in 2008 (2) and the end PCV7 vaccine shortages at the national level (3). The introduction of PCV13 in 2010 among children (4) most likely allowed the adult PP decline from 2010 to 2013 to be sustained. Even though both PP and IPD trends show a marked and significant decline from 2010 to 2013, IPD trends from 2000 to 2009 were variable. The overall IPD trend showed a significant rise in IPD rates of about 3% per year while subpopulation trends showed either no significant change or a small annual percent increment in rates. From 2010 to 2013, IPD trends show a marked decline, however the annual percent decline is not as dramatic as the decline seen in PP trends of about 15% to 20% annual decline in rates depending on subpopulation group. These results highlight the indirect benefit adult received from the introduction of children conjugate vaccines in the population.

Chapter four demonstrated that the current surveillance system in Arkansas has low sensitivity and thus may be under-reporting adult IPD cases. However, substantial improvements were observed, especially after the introduction of the NBS a web based system that replaced the former mail and phone based system. These results demonstrate that reaching an all-inclusive surveillance system can be accomplished, especially with further education of health care workers on which conditions and why have to be reported.

5.2. Future Research

Adult IPD and PP trends differ and this observations merits further study. From 2010 to 2013, trends are similar in shape but differ in magnitude. Considering the serotype distribution is related to age and clinical manifestation (5, 6), it is possible that the impact of conjugate pneumococcal vaccines may have varying effects on different disease processes. If the serotypes found in the conjugate vaccines are more likely to cause pneumonia, then the "herd effect" would more effectively reduce the transmission of serotypes responsible for pneumonia and a greater declines in rates would be observed than in IPD rates. However, serotype information for each infection event would be necessary to explore this hypothesis.

Another interesting difference that was observed is that the PP rates show a sustained decline while IPD rates show a slight decline followed by small incline in the pre-PCV13 years (2000 to 2009). This difference may suggest that the "herd effect" on IPD rates was short in duration compared to the effect on PP. Other studies which have also observed this sudden rise have suggested a serotype replacement phenomenon in which serotypes found in the vaccines are wiped out and other serotypes replace them (7, 8). Results from this study beg the question of why this serotype replacement is not noticeable in adult pneumococcal pneumonia hospitalization trends. Again, this difference may be explained by differences in the serotype distribution of each type of infection. Exploring differences at the serotype level could shed light on the underlying serotype distribution under which the serotype replacement takes place.

These differing trends could also be explained by differences in the characteristics of the populations captured in each sample. Based on the patient demographics for each disease (Tables 2.1 and 3.2) studied, these two samples do not appear to be drastically different. However, there may be differences in the distribution of comorbidities such as AIDS or smoking behavior in each disease group. A previous study showed that some serotypes are associated with PD risk

factors such immunosuppression (9, 10). There may also be serotype variability in the two samples based on the geographic location of patients. In this study a greater proportion of IPD than PP cases came from rural counties (Tables 2.1 and 3.2). Thus, it would be interesting to understand how serotypes are distributed in each disease group given that rural counties are significantly older than urban counties (11) and serotype distribution varies by age (5, 6).

Another striking finding that spurred further questions are the trends identified among Blacks with both PP and IPD. Out of all sub-population groups evaluated, Blacks in both age groups showed the steepest declines in pneumococcal pneumonia rates throughout the entire study period. Blacks with IPD in the 18 to 64 age groups also showed the steepest decline than any other subpopulation evaluated. This was quite an unexpected result given the extensive literature on subpar vaccination access among racial and ethnic minorities (12, 13) and higher PD rates reported among Blacks in the ABCs (14). In light of all this research, this finding suggests that the lower PD risk among Blacks may be unique to the context of Arkansas and merits further study. Of special interest would be to learn about vaccination rates among Black children compared to White in Arkansas, since this could impact the protection conferred by the "herd affect" to adult populations. Also the distribution of colonizing serotypes among Black and White children would be useful to understand the impact of vaccinations in each racial group.

On the other hand, it is also possible that our data sources are not capturing Black cases because they do not present to hospitals due to lack of insurance or other health care access issues. A study on African-American health in Arkansas in 2010 showed that 28.0% of Blacks were uninsured, which was significantly higher than the uninsured rate among Whites (19.7%) (15). A preliminary analysis of this HDD data set revealed that only about 1% of PD cases were uninsured. Underreporting of Blacks in HDD could lead to under-calculation of incidence rates

in this group, thus this bleak possibility must not be discarded.

Another issue that highlights the uniqueness of the Arkansas population is the low adult IPD incidence rates throughout the entire study period reported in this study, especially when compared to the national estimates from the ABCs (Figure 5.1) (14). These differences have been noted before. A study by Rosen et al. (7) showed that each population surveilled by the ABCs spanning 8 states in the US showed diverse IPD trends and a different magnitude of IPD disease burden. However, this observation is important and merits further research, because it may suggest that there are unique characteristics in the Arkansas population that may be able to contain the disease burden to a significant lower level than the national estimates. Understanding the cause of these differences may help to guide future immunization policy at the national level.

Issues of underreporting were deeply felt when we found that the adult IPD surveillance system had less than 50% sensitivity over a span of ten years. However, it is interesting to note that all hospitalized cases matched to the surveillance system had laboratory tests indicating that *Streptococcus pneumoniae* was successfully isolated from a sterile body site. This raises an important question about the validity of cases in HDD. Is it possible that adult PD cases that did not match to surveillance system cases did not have confirmatory lab results? If so, we could be under-estimating sensitivity because our gold standard source of cases has too many false-positives.

Despite being an extensive repository of information, HDD is designed for financial rather than epidemiologic research. A major drawback is that it lacks important clinical information such as symptoms and laboratory tests. This makes validation of any condition difficult if based solely on ICD-9-CM codes in HDD. Errors in diagnoses coding may occur due to many reasons including poor communication between patient and physician, availability of

tests, transcribers' ability to read physicians' notes and translate them into an ICD-9-CM code and many others (16). A recent meta-analysis found that the median diagnosis accuracy in administrative data for determining a true condition based on a clinical evaluation was 80.3% (17). Knowing the limitations of HDD should drive the efforts to ensure a fully functional surveillance system in order to accurately describe the epidemiology and trends of diseases in a population in order to be used effectively to guide immunization policy.

5.3. Conclusion

The results of this dissertation have helped to provide a baseline understanding of the epidemiology of adult PD in Arkansas and how this has changed as a result of the introduction of children pneumococcal vaccines. It has also spurred many questions in relation to the uniqueness of the Arkansas population which should be addressed in order to develop targeted adult vaccination campaigns. Studies like the ones presented here highlight the need of population-specific assessments to combat vaccine preventable diseases. Understanding the recipient population is just as important as delivering vaccines for immunizations to be effective. The assessment of the state's IPD surveillance system provides insight unto the usefulness of this system to help guide immunization policies. Adult PD trends are expected to continue to shift especially after the ACIP recommended the routine use of PCV13 among adults aged 65 years and older in late 2014 (18). Thus, continue surveillance is critical and a functional surveillance system is absolutely necessary in order to continue to monitor trends and be able address the public health needs of this population.

5.4. Figure

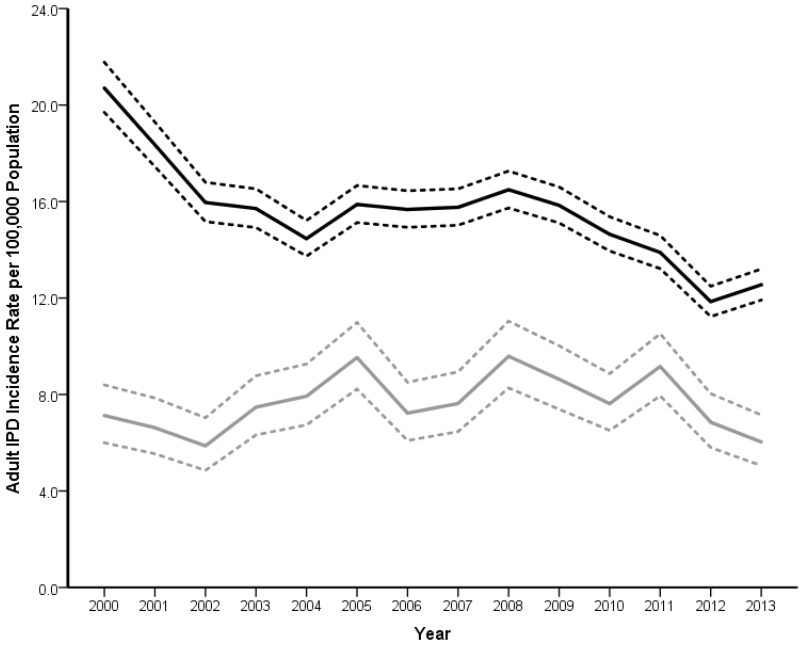

Figure 5.1. Annual adult IPD (18 years and older) incidence rates per 100,000 population in Arkansas and in the ABCs populations from 2000 to 2013.

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