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APPROVAL SHEET

CHANGING EPIDEMIOLOGY OF INVASIVE PNEUMOCOCCAL DISEASE AMONG OLDER ADULTS IN THE POST 13-VALENT PNEUMOCOCCAL CONJUGATE VACCINE ERA IN ATLANTA'S METROPOLITAN STATISTICAL AREA

By

Marissa Joy Tracy

Degree to be awarded: Master of Public Health

Department: Epidemiology

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Thesis Committee Chair: Dr. Robert Bednarczyk

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By

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Bachelor of Science

University of Pittsburgh

2015

Thesis Committee Chair: Dr. Robert Bednarczyk

An abstract of
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ABSTRACT

CHANGING EPIDEMIOLOGY OF INVASIVE PNEUMOCOCCAL DISEASE AMONG OLDER ADULTS IN THE POST 13-VALENT PNEUMOCOCCAL CONJUGATE VACCINE ERA IN ATLANTA'S METROPOLITAN STATISTICAL AREA

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Background- In 2010, a 13-valent pneumococcal conjugate vaccine (PCV13) was introduced in the U.S. in children 2> years old resulting in dramatic reductions in invasive pneumococcal disease (IPD) in children 5> years old and adults ≥65 years old. In 2014, the Advisory Committee on Immunization Practices (ACIP) recommended PCV13 use in adults ≥65 years old. IPD trends from 2008-2017 were evaluated to investigate the impact of changing vaccination practices on the epidemiology of IPD in adults ≥65 years old in Atlanta's Metropolitan Statistical Area (MSA).

Methods- Laboratory- and population-based surveillance data collected by CDC's Emerging Infections Program (EIP) / Active Bacterial Core Surveillance (ABCs) were used to calculate race-, sex-, age-, and serotype-specific IPD incidence from 2008-2017 among older adults in the Atlanta MSA. IPD-related mortality was modeled using logistic regression to evaluate risk-factors for death among older adults in the late-PCV13 era (2015-2017).

Findings- Overall IPD incidence declined significantly in older adults from 2008-2017. Race- and serotype-specific IPD rates also declined significantly. Disease burden shifted from white females in the pre-PCV13 era (2008-2010) to black males in the post-PCV13 era (2011-2017). By 2013, the rate decline in whites surpassed the rate decline in blacks. PCV13 serotypes declined significantly during the time frame. The rate ratio of PCV13 serotype disease compared to non-vaccine serotypes of disease dropped from 1.5 in the pre-PCV13 era to 0.48 in the late-PCV13 era. Modeling for IPD-related death revealed that receipt of any pneumococcal vaccine and black race had a protective effect against mortality whereas ICU admission and septic shock were associated with increased risk of death.

Interpretation- Vaccination plays a critical role in reducing IPD and IPD-related mortality in adults ≥65 years old. Efforts to increase PCV13 adherence in children 2> years old and PCV13 uptake in older adults is essential to further reduce IPD rates, particularly in black persons. More research must but done to understand the impact of PCV13 use in older adults ≥65 years old.

Key words- *Streptococcus pneumoniae,* invasive pneumococcal disease, pneumococcal vaccines, pneumococcal conjugate vaccine, serotypes, epidemiology, mortality

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Disclaimer:

The primary dataset used in this project was collected by the Georgia Emerging Infections Program (GAEIP). The GAEIP was not involved in the analyses presented in this thesis.

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Contents

BACKGROUND & LITERATURE REVIEW

Introduction: epidemiology and impact of the pneumococcus

Streptococcus pneumoniae, also known as the pneumococcus, is a major cause of pneumonia, meningitis, and many other clinical syndromes. Pneumococcal diseases are widespread in both developed and developing countries, causing 1.6 million deaths annually according to the World Health Organization (WHO).[1, 2] *S. pneumoniae* can cause both invasive disease (e.g. meningitis and bacteremia) and non-invasive disease (e.g. ottis media and non-bacteremic pneumonia). Young children (≤2 years old), older adults (≥65 years old), and individuals with immunocompromising conditions, weakened immune systems, or specific comorbidities are at greatest risk for invasive disease.[1, 3, 4] Invasive pneumococcal disease (IPD) is responsible for a substantial burden of disease and health-care costs in both developed and developing countries.

The epidemiology of IPD varies substantially throughout the world due to differences in vaccination practices and dominating serotypes in circulation. In the United States (US), pneumococcal disease is concentrated among the elderly – about 60% of hospitalized pneumococcal pneumonia patients are adults aged ≥65 years old.[5] Pneumococcal pneumonia leads to about 300,000-600,000 hospitalized cases each year in the elderly; case fatality within this population ranges from about 2.6 cases/100,000 population to 8.56 cases/100,000 population.[3,6]

Before the widespread use of pneumococcal conjugate vaccines (PCVs) in children, IPD incidence rates among adults 50 years and older was reported as 40.8 cases/100,000 population in 1998-1999. In 2002-2003, IPD incidence in adults ≥65 years old was reported as 41.7

cases/100,000 population.[7] Introduction of the 7-valent pneumococcal conjugate vaccine (PCV7) for use in children in 2000 and the 13-valent pneumococcal conjugate vaccine (PCV13) in 2010 led to a dramatic reduction in IPD incidence in both children and adults.[7, 8] In 2016, IPD incidence in the elderly dropped to 24 cases/100,000 in surveillance sites across the US.[6]

According the US Census Bureau, by 2035 the number of adults of retirement age will exceed the amount of children ≥17 years old (78 million vs. 76.7 million, respectively).[9] Considering both inpatient and outpatient pneumococcal pneumonia treatment of older adults, one study predicted that the total direct costs for this additional burden will increase by 25% from 2020 to 2030 ($3.3 billion vs. $4.2 billion).[5] As the US population continues to age, it is important to study the impacts of IPD morbidity and mortality among the elderly to prepare for the effect of this demographic shift on the healthcare system.

Risk factors for IPD

Age and underlying conditions

Surveillance activities have demonstrated that young children (aged ≤5 years) and older adults (aged ≥65 years) experience the highest rates of IPD. Although healthy adults may become ill with IPD, those that are older and suffer from multiple underlying conditions are at greatest risk of infection. Older adults are vulnerable to an age-associated deterioration of their immune system, called immunosenescence, making them more vulnerable to infection.[10]

The Advisory Committee on Immunization Practices (ACIP) defined two risk profiles for older adults based on the type of underlying conditions experienced. Older adults 'at risk' for infection are considered immunocompetent persons with one or more of the following 'at risk' conditions.[11, 12] 'At risk' conditions include chronic conditions (chronic heart disease, chronic

lung disease, chronic liver disease, diabetes mellitus) and preventable behavioral choices (alcohol and tobacco use).[10, 13, 14] Older adults that are at 'high risk' for infection are immunocompromised or immunosuppressed persons with one or more of the following conditions: cerebrospinal fluid leak, cochlear implant, functional or anatomic asplenia, HIV/AIDS, chronic renal failure, nephrotic syndrome, leukemia, lymphoma, solid organ transplant, or multiple myeloma.[11, 12]

Many older adults experience multimorbidity, defined as a patient with two or more comorbid underlying conditions. Multimorbidity puts older adults at increased risk of IPD and negatively impacts health outcomes. In 2009, IPD incidence for all serotypes remained higher among individuals with multimorbidity compared to those with no underlying conditions.[13]

An analysis of community acquired pneumonia (CAP) revealed three common comorbidities seen in adults ≥65 years old: diabetes, chronic heart disease, and chronic obstructive pulmonary disease (COPD).[11] When experienced together, these three conditions showed an odds ratio (OR) of ≥7.5 for CAP; smokers with these three conditions had an even greater risk for CAP with an OR of ≥8.5.[11] As the percentage of US adults living with multimorbidity continues to rise in the elderly population, it is important to consider how this affects susceptibility to IPD.

Racial and socioeconomic disparities

Racial and socioeconomic disparities also play a role in IPD risk in older adults. In 2004, Kyaw et al. demonstrated that IPD incidence in older black adults was approximately twice as high as seen in older white adults. Comparing older adults with 'at risk" and 'high risk' conditions by race, blacks had a 2-7 fold greater IPD incidence than whites.[15] Previous studies have indicated that socioeconomic factors, including median household income and education

level, are associated with incidence of IPD.[16-18] In 2010, a multivariable poison regression analysis of invasive community acquired bacterial pneumonia incidence found significant 2-way interactions between race and age group and census tract poverty level and age group.[16] Additionally, blacks had a higher incidence of bacterial pneumonia at all census tract levels in comparison to whites and hispanics. This social gradient is also seen in other bacterial and viral pathogens that disproportionately affect the elderly.[19-21] Analysis of socioeconomic data is vital to better understand disparities in IPD related mortality.

Bacterial characteristics of the pneumococcus

Pneumococci are lancet-shaped gram-positive bacteria that grow in pairs or short chains.[22] At least 97 serotypes of *S. pneumoniae* are recognized today.[3, 10] Regional differences in pneumococcal serotype distribution and antibiotic resistance profiles are seen globally.[1] *S. pneumoniae* is spread by fomites and person-to-person contact with aerosolized droplets.[3]

The transmission of *S. pneumoniae* is complex. First, the bacteria colonize the nasopharynx of the host. During colonization, pneumococci are capable of forming biofilms in the nasopharynx. Key structural components of *S. pneumoniae* enable pneumococci to asymptomatically reside in the host nasopharynx, called carriage. During carriage, *S. pneumoniae* may cause minor infections such as otitis media or sinusitis. Prolonged evasion of the host immune system allows the pneumococcus to become pathogenic and spread further into the body. This horizontal dissemination of *S. pneumoniae* from the host nasopharynx and lower airways into other organs and tissues enables these bacteria to cause serious invasive diseases such as pneumonia, septicemia, and meningitis. In severe cases, IPD can cause death. Studies indicate that approximately 10% of patients with IPD die of their illnesses each year.[1, 3]

Nasopharyngeal (NP) carriage is a necessary precursor of IPD. Carriage most commonly occurs in young children, but can also occur in adolescents and adults with certain underlying conditions. Children that are <6 years old, have young siblings, and attend day care facilities are at greatest risk for NP carriage of *S. pneumoniae*.[1] The nasopharynx provides this pathogen an ideal environment to proliferate and keep a low profile before spreading to other parts of the body. Additionally, carriage promotes the transmission of *S. pneumoniae* to other susceptible hosts.

Immunocompetent adults are at lowest risk for NP carriage of *S. pneumoniae.* Their robust immune systems can quickly identify and respond to the pneumococcus before it is able to become pathogenic and cause invasive disease. Clearance of pneumococci is challenging; humoral and cell-mediated immune responses are utilized. Pneumococci recognized by pattern recognition receptors trigger the host immune system to release various bactericidal immune factors (including tumor necrosis factor-α, interleukin-1β, granulocyte-colony stimulating factor, and interferon-γ). This immune response marks the bacteria for destruction and promotes phagocytosis and oxidative burst, allowing for clearance of the pathogen.[1]

Individuals with underdeveloped, weakened, or deteriorating immune systems are most vulnerable to *S. pneumoniae*.[3] Pneumococcal structural components and virulence factors elevate the pathogenicity of these highly adaptable bacteria. The polysaccharide capsule, choline-binding proteins (CbpA, LytB, LytA, CbpC, and CbpG), neuraminidase, and non-classical surface proteins help pneumococci colonize and adhere to the host nasopharynx. Production of pneumolysin, autolysin, and hydrogen peroxide induces cell-lysis, allowing for the continuous spread of pneumococci from host to host. *S. pneumoniae* is also able to directly attack the host

immune system by using enzymes, such as IgA protease, that hinder complement and cell phagocytosis.

The development and implementation of pneumococcal vaccines has successfully reduced vaccine type disease in immunized populations and reduced pneumococcal carriage in children under 5 years old. Consequently, protection against IPD has extended to non-immunized populations by reducing disease among all ages via herd immunity.[10] Use of pneumococcal vaccines has also reduced the prevalence of antibiotic non-susceptible strains of *S. pneumoniae*.[23] In 2016, penicillin-resistance and erythromycin-resistance among isolates collected via the Center for Disease Control and Prevention (CDC) Emerging Infections Program (EIP) has been reported as 2.2% and 30.7% respectively.[6] Despite these successes, challenges to disease prevention continue.

Vaccination strategies for pneumococcal disease prevention

Two types of vaccines are currently in use to prevent IPD: polysaccharide and conjugate vaccines. Different populations benefit from vaccination with one or both of these vaccines. Pneumococcal polysaccharide vaccines (PPVs) stimulate antibody production against select pneumococcal capsular polysaccharides via T-cell-independent mediated immune response. Because T-cell independent immune response requires a mature immune system, polysaccharide vaccines are most effective in adults. Pneumococcal conjugate vaccines (PCVs) similarly target select pneumococcal capsular polysaccharides, however, purified polysaccharides are conjugated to a carrier protein, CRM197. Conjugation of polysaccharides to proteins alters the subsequent immune response, stimulating a T-dependent (T-helper-cells) response. Primary vaccination with PCVs followed by booster vaccination in series generates a lasting, robust immune response among infants.[24]

In the US, the ACIP routinely reviews current literature and IPD monitoring data to provide recommendations on the appropriate vaccination recommendations in different US populations. Vaccination efforts against IPD date back to the 1970s. In 1974, the first polysaccharide vaccine licensed for use in the US was PPSV14.[24] An updated polysaccharide vaccine including coverage against nine additional serotypes, PPSV23, was recommended for use in adults ≥65 years old in 1983. In 2000, the first pneumococcal conjugate vaccine licensed for use in the US was PCV7.[25] A four-dose PCV7 vaccination schedule was recommended for use in infants and young children. In 2010, PCV13 replaced PCV7 in the childhood vaccination schedule.[26] PCV13 included the original seven serotypes in PCV7 plus six additional serotypes of pneumococcal disease with increased incidence in the post PCV7 era.

Routine use of PCVs in children has profoundly reduced carriage of vaccine-type serotypes of IPD; consequently, pneumococcal transmission has substantially declined.[13] The widespread use of PCV7 among children in the US led to substantial change in the epidemiology of IPD among all age groups. The introduction of PCV13 immunization continued this trend. This is due to herd immunity, an indirect benefit of PCV vaccination programs, which is achieved when a high proportion of a population is vaccinated (and thus immune to common serotypes of *S. pneumoniae*) and subsequently provides protection to those who have not been vaccinated.[10, 24, 27]

For 30 years, the only pneumococcal vaccine recommended for use in adults was PPSV23. Researchers found that PCV13 vaccination followed by PPSV23 vaccination resulted in continued immunogenicity and anti-pneumococcal responses when compared to vaccination with PPSV23 alone.[28] Following the results of the Community-Acquired Pneumonia Immunization Trial in Adults (CAPiTA) and the observed declines in IPD rates among US adults

as a result of PCV13 herd effects, the ACIP elected to recommend one dose of PCV13 followed by a dose of PPSV23 in adults aged ≥65 years old in 2014.[24, 29, 30] In 2015, the recommendation was updated to clarify the optimal vaccination sequence and schedule.[12]

Conjugate vaccination is a great option for those adults with multimorbidity as polysaccharide vaccine efficacy is lower among those with comorbid conditions than healthy adults.[13] In the conjugate vaccine era, it is essential to target high risk individuals with multimorbidity to seek the greatest benefit of vaccination.[7]

Thesis rationale and objectives

Reducing invasive pneumococcal infections among adults aged ≥65 years old is a listed objective in *Healthy People 2020*.[31] Additionally, *Healthy People 2020* sought to increase the percentage of adults aged ≥65 years old who are vaccinated against pneumococcal disease to 90%. As the ACIP gears up to re-evaluate the current vaccination strategy for pneumococcal disease prevention in the elderly, it is essential to review the current research, epidemiology, and progress towards reaching the goals set in the *Healthy People 2020* framework.

The purpose of this analysis is to 1) examine changes in IPD trends considering changing pneumococcal vaccination practices among adults aged ≥65 years on the epidemiology of race-, sex-, age-, and serotype-specific rates in the Atlanta Metropolitan Statistical Area (MSA) from 2008-2017 and 2) model the risk factors for death to determine high risk groups and conditions for IPD within this population.

METHODS

Study Population

IPD cases were identified by CDC EIP Active Bacterial Core surveillance (ABCs), a long-standing surveillance system that collects information on cases of invasive bacterial infections caused by pathogens of public health importance.[32] ABCs active, population- and laboratory-based surveillance is conducted in ten sites across the US: California, Colorado, Connecticut, Georgia, Maryland, Minnesota, New Mexico, New York, Oregon, and Tennessee. Georgia EIP (GAEIP) works in collaboration with Emory University, the Georgia Department of Public Health, and hospitals in the greater Atlanta area to attain timely case ascertainment. This analysis is limited to cases residing in Atlanta's twenty county MSA by GAEIP. US census data was used to estimate the population size in this catchment area.

IPD cases were defined as isolation of *S. pneumoniae* (SPN) from a normally sterile site such as blood, cerebrospinal fluid, or pleural fluid. Second episodes within seven days of the first positive SPN culture were omitted. Since hospitals in the area do not routinely use culture independent diagnostic testing (CIDT) methods (e.g., PCR) alone for IPD diagnosis, IPD cases that only tested positive by a CIDT were not included this analysis. Laboratory audits were reviewed to ensure complete case reporting.

Cases aged ≥65 years old with a positive SPN culture from 2008-2017 were included in this analysis. The time period 2008-2017 was chosen due to significant changes in vaccination guidelines for pneumococcal pneumonia in children and adults.

Core Variables

Demographic, clinical, and outcome information were abstracted from the medical chart by GAEIP personnel. Data was recorded onto a standardized case report form provided by CDC. Age was stratified into two groups: 65-74 years old and 75 years and older. Race analysis was performed for blacks and whites only due to small numbers in other groups. Underlying conditions considered as indications for pneumococcal vaccination by the ACIP and collected by GAEIP ABCs core surveillance were included in this analysis. Pneumococcal vaccination status and vaccine type were recorded for cases in surveillance years 2014-2017. Vaccination date was not collected on the CDC case report form.

The time period for analysis was broken up in two different ways: surveillance year and study period. Three study periods were defined based on changing vaccination recommendations for PCV13. Period 1, the pre-PCV13 era, includes surveillance years 2008-2010. Period 2, the early PCV13 era when PCV13 became recommended for children, includes surveillance years 2011-2014. Period 3, the late PCV13 era when PCV13 became recommended for routine use in adults aged ≥65 years old, includes surveillance years 2015-2017.

Isolates were sent to CDC's *Streptococcus* Laboratory for serotyping by the Quellung reaction. In this analysis, serotypes were assigned to the following categories: 1) PCV7-types (serotypes 4, 6B, 9V, 14, 18C, 19F, 23F, and 6A), 2) PCV13-types (serotypes 19A, 7F, 5, 3, and 1 [which are serotypes unique to PCV13 and unaffected by PCV7 vaccination] and 6C), 3) PPV11-types (serotypes 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, and 33F, which are serotypes unique to PPV23), and 4) non-vaccine-type serotypes. Serotype 6A is categorized with PCV7 serotypes due to demonstrated cross-reactivity with PCV7 6B antigen and past-precedent.[8, 13] Serotype 6C is categorized with PCV13 serotypes due to demonstrated cross-

reactivity with PCV13 serotype 6A; declines in serotype 6C disease rates have been observed since the introduction of PCV13 immunization programs in the US.[33] Cases without an isolate available for serotyping were excluded from the serotype portion of this analysis.

Statistical Analyses

Descriptive statistics for age, race, sex, outcome, infection type, underlying conditions, and year were examined in univariate analysis to look at IPD trends. To protect confidentiality of the eldest cases, age was set to a standardized 85 years for all cases aged ≥85 years old at the time of their IPD culture.

Incidence rates for age, race, and sex were calculated by surveillance year and study period. Incidence rates for vaccine-type (PCV7, PCV13, and PPV11) and non-vaccine-type serotypes were compared by study period and age. All incidence rates were reported as number of cases per 100,000 population. Statistically significant changes in IPD rates over time were determined by Chi-square test for trend. Rate ratios between surveillance years and study periods were calculated via Poisson regression.

Variables found to be significantly associated with IPD mortality in univariate analysis underwent backward variable selection to build a logistic regression model for IPD mortality in adults aged ≥65 years old. Key clinically relevant variables were also entered into the initial model to search for possible interaction between variables. Because vaccine data was only available for cases from 2014-2017, only Period 3 cases were included in the IPD mortality model to determine current risk factors associated with death in the late PCV13 era.

All statistical analyses were performed using SAS Version 9.4 (SAS Institute Inc, Cary, NC). Significance was defined as two-tailed p values less than 0.05.

RESULTS

There were 1,547 cases of IPD identified in adults aged ≥65 years old living in Atlanta's 20-county MSA from 2008-2017 (**Table 1A-B**). Median age of elderly IPD cases was 75 years old. The proportion of adults aged 65-74 years compared to adults aged 75+ years was nearly even (48.4% vs. 51.6%). Cases were more likely to be female (55.5%) and white (71.0%). The case fatality rate was 14.9%.

The most common infection type among cases was pneumonia (75.9%), followed by septic shock (12.9%), bacteremia without focus (11.4%), and meningitis (4.7%). Most cases (72.4%) had multimorbidity. Emphysema/COPD (33.2%), diabetes (30.3%), coronary artery disease (25.6%), and heart failure (22.8%) were the most common underlying conditions among cases (**Table 2**).

Nearly all cases (94.1%) were hospitalized at the time or within thirty days of IPD culture. Of those hospitalized, the median length of stay was seven days and 32.4% were admitted to an intensive care unit (**Table 1A-B**).

In cases where isolates were available, serotyping was performed. PCV7 serotypes accounted for 3.8% of cases, PCV13 serotypes accounted for 31.4% of cases, PPV11 serotypes accounted for 28.6% of cases, and non-vaccine serotypes accounted for 36.2% of cases.

Vaccination data was not routinely collected through GAEIP surveillance until 2014. Among cases in Period 3 (2015-2017), 43.7% of cases were vaccinated against *S. pneumoniae.* Most cases were vaccinated with PPSV23 alone (26.7%). Only a small fraction of cases (4.8%) had received both PPSV23 and PCV13 – the ACIP recommended vaccination schedule for elderly adults since 2014 (**Table 3**).

The overall IPD incidence rate declined significantly in elderly cases (p=0.0007) from 37.53 cases per 100,000 population in 2008 to 23.68 cases per 100,000 population in 2017 (**Tables 4A-C**). The highest rate of 44.56 occurred in 2009 and the lowest rate of 22.27 occurred in 2016. Declines in trends were not significant by age or sex **(Figure 1A and 1C).** The most dramatic decrease occurred in elderly males, where the baseline IPD rate in 2008 was 42.45 cases per 100,000 population and dropped to 22.24 cases per 100,000 population in 2017**.** Declines in trends were significant by race (p_{white} =<0.0026, p_{black} =<0.0077). Although rates declined in both blacks and whites during the time frame, the rate decline in whites surpassed the rate decline in blacks by 2013 **(Figure 1B).**

During the ten year time frame, burden of disease shifted from white females in the pre-PCV13 era to black males in the post-PCV13 era (**Figure E**). Among whites, rates in all females and females aged ≥75 years old declined significantly ($p_{white+\ female}$=<0.0014, $p_{white+\ female+age\ \geq 75}$ =0.0253) (**Table 5C; Figure 1F**). Similar trends were observed in blacks; rates in all black females and black females aged ≥75 years old declined significantly during the time frame ($p_{black+\ female}$=<0.0023, $p_{black+\ female+age\ \geq 75}$ =0.0087) (**Table 5C; Figure 1G**). White females 65-74 years old consistently had the lowest incidence rates during the ten year time frame (29.96 in 2008 to 15.21 in 2017). Black females aged ≥75 years and black males aged ≥75 years had the highest rates during the time frame.

Incidence rates by vaccine group were analyzed to look for trends in IPD serotype over time (**Tables 6A-B, Figure 3A**). Rates declined significantly in all vaccine groups except for PCV7 serotypes (**Table 7C**). PCV7 serotypes had the smallest rates, with serotypes 19F, 6A, and 6B accounting for the majority of PCV7 cases. PCV13 serotypes had the highest rates of disease in the pre-PCV13 era; non-vaccine serotypes had the highest rates in the post-PCV13 era.

PCV13 serotypes exceeded the incidence of PPV11 serotypes in the pre-PCV13 era (**Figure 2A**). After the introduction of pediatric PCV13 immunization in 2010, PCV13 serotype disease rapidly declined. In 2011, PCV13 serotype disease incidence dropped below PPV11 serotype incidence. When geriatric PCV13 immunization began in 2014, PCV13 serotype disease rates began to stabilize in the following years. In the post-PCV13 era, serotypes 3 and 19A were responsible for most PCV13 type disease; serotype 22F caused the majority of PPV11 type disease during the same time frame.

Vaccine group incidence was then stratified by age to see how age-specific IPD serotype rates changed over time. IPD incidence was higher in adults aged ≥75 years old than adults 65-74 years old in all vaccine groups (**Figures 2B-E).** Rates declined significantly in all serotype groups among adults aged ≥75 years old, whereas rate declines in adults 65-74 years old where only significant for PCV13 and non-vaccine serotypes (**Tables 7A-C**).

To assess risk factors for IPD mortality in elderly cases, a logistic regression model was created. Modeling was limited to IPD cases occurring in Period 3 (2015-2017) so that vaccination status could be included as the primary exposure. Variables were screened for inclusion via chi-squared test for association; variables found to be significantly associated with death were automatically included in the model (**Table 8 A-B**). Select clinically significant variables were entered into the model as well (white race, sex, COPD/emphysema, congestive heart failure, diabetes, alcohol abuse, current smoker). Backwards elimination was used to model IPD related mortality in elderly adults.

The final model had a goodness-of-fit statistic of 0.601 (**Table 9**). Two factors were found to be associated with an increased risk of death: ICU admission (OR=4.85, p=<0.0001) and septic shock (OR=1.91, p=0.009). Factors associated with a decreased risk of death were

black race (OR=0.19, p=0.004) and history of vaccination with any pneumococcal vaccine (OR=0.50, p=0.018). Two interaction terms were kept in the final model: white race with septic shock and black race with current smoker. White race and current smoker were kept in the final model despite their individual lack of association with mortality because of their involvement with interaction. Although black race and septic shock were part of interaction terms, odds ratios were calculated in SAS by holding current smoker and white race at a constant.

DISCUSSION

This was the first study to analyze changing IPD trends among elderly persons in the US since the ACIP recommended PCV13 vaccination in adults aged ≥65 years old. This analysis also investigated risk-factors for IPD-related mortality, a current subject of interest among researchers and clinicians.

In the past decade, the epidemiology of IPD in adults aged ≥65 years old has changed substantially. Overall IPD incidence has declined by 37% and disparities in race and sex have narrowed. White females experienced the greatest burden of disease in the pre-PCV13 era. After pediatric PCV13 immunization began in 2010, all race- and sex- specific rates declined dramatically. In 2013, disease burden shifted to black males. At its greatest disparity, incidence in black males was twice that in white females. This gap did not narrow until 2016, nearly two years after PCV13 immunization was recommended for use in older adults aged ≥65 years old.

Trends in IPD incidence in the elderly: racial disparities

While racial disparities in IPD have narrowed since the use of PCVs, disparities continue to persist today. Trends in pneumococcal vaccination in pediatric and elderly populations play an important role. Although the 4-dose pediatric PCV13 immunization series led to dramatic IPD declines in both pediatric and elderly populations, local variation in pediatric vaccine adherence (completion of the 4-dose series) has contributed to racial disparities in IPD.

Racial disparity in pediatric PCV vaccination adherence has been observed across the US. In Connecticut, pediatric PCV7 vaccination uptake varied significantly by zip code. Zip codes with lower PCV7 uptake were significantly more likely to have a higher proportion of black or hispanic children and increased rates of PCV7-type IPD in children and elderly adults.[34]

Two studies found that poverty level is the primary indicator for racial differences in pediatric PCV vaccination adherence.[35, 36] Consequently, IPD incidence in children and elderly remain elevated in impoverished, black communities where pediatric PCV vaccination adherence is suboptimal.[34, 35, 37]

Racial disparity in pneumococcal vaccination is also seen in elderly adults despite the ACIP recommendation for a 2-step vaccination series. Data from the 2015 National Health Interview Survey found that pneumococcal vaccination coverage in adults aged ≥65 years old was lowest among racial minorities and impoverished populations.[38] In addition to socioeconomic factors, cultural attitudes toward vaccination and preventative care contribute to racial disparities in adult pneumococcal vaccination uptake.[39, 40] A recent study investigating neighborhood influences on seasonal influenza vaccination in older black adults in Georgia found that positive vaccination attitudes and having health insurance were significantly associated with greater influenza vaccination uptake.[41] Use of PCV13 in adults has demonstrated efficacy in preventing both invasive and non-invasive pneumococcal disease in elderly adults[42] whereas PPV23 provides expanded coverage of many additional IPD serotypes not included in PCV13. Suboptimal vaccine adherence may hinder the potential benefit of this 2-step vaccination series.

Trends in IPD incidence in the elderly: serotype group

Trends in serotype were investigated by observing changes in vaccine-serotype and non-vaccine serotype group incidence over time. All serotype groups (except PCV7 serotypes) declined significantly during the time frame; the largest declines occurred in PCV13-type disease. Declines in serotype 6C, a non-vaccine serotype, were observed in the post-PCV13 era due to cross-protection by PCV13 serotype 6A. The greatest reductions in PCV7-type disease in

adults aged ≥65 years old occurred in the immediate years following the introduction of pediatric PCV7 programs in 2000 and thus was not captured in this study.[43] Analysis of non-vaccine serotypes did not reveal any emerging serotypes affecting this population. Of note, a slight uptick in PCV13-type disease occurred in 2017.

Serotypes 3 and 19A accounted for nearly all PCV13 type cases seen in this analysis. Challenges in preventing IPD caused by serotypes 3 and 19A have been well-documented. Serotype 3 is known to be associated with PCV13 vaccine failure. Multiple studies have found that PCV13 is ineffective against serotype 3 NP colonization and invasive disease in children.[8, 44, 45] Serotype 19A rapidly emerged following the introduction of PCV7 and was consistently identified as the most frequent serotype of childhood IPD.[46] Incidence of this serotype dramatically reduced in children aged <2 years and adults aged ≥65 years with the introduction of PCV13 in 2010.[47] The recent uptick in serotype 19A could be due in part to incomplete pediatric PCV13 adherence; previous research has indicated that PCV13 efficacy against IPD caused by serotype 19A is reduced with incomplete pediatric vaccine adherence.[35]

Risk factors for IPD-related mortality

Risk factors for IPD-related mortality were analyzed in elderly IPD cases in Period 3, the late PCV13 era. Risk factors entered into the logistic regression model included demographic characteristics, infection type, vaccine history, admission types, and underlying conditions.

Two factors were found to be associated with increased risk of death – ICU admission and septic shock. Both of these factors indicate increased severity of infection that would universally increase risk of death for many infections. Thus, this finding may represent confounding rather than true risk-factors for IPD-related mortality.

The association between black race and a decreased risk of death was an unexpected finding. This result is most likely explained by barriers to care or decreased healthcare utilization. It is also possible that an unidentified confounder may play a role. In contrast with this analysis, a recent study found that black individuals had a significantly greater risk for IPD-related mortality than non-black individuals.[48]

Receipt of any pneumococcal vaccine was found to be associated with decreased risk of death. There is substantial evidence that PPV23 vaccination reduces severity of pneumococcal infections and chance of death among older adults aged ≥65 years old.[49] Additionally, studies have found that pediatric PCV13 vaccination led to decreases in IPD mortality in elderly populations, another indirect benefit of pediatric PCV13 vaccination programs.[50] The impact of direct PCV13 vaccination in adults on mortality is still uncertain due to slow vaccine uptake and limited data available since the ACIP recommendation in 2014.

Two interaction terms were included in the model: white race with septic shock and black race with current smoker. The significance of these interaction terms is unclear. There were no previous studies that reported similar findings. It is possible that both of these effects are tangentially related to poverty-level. Prevalence of cigarette smoking is inversely related to poverty level and impoverished communities often have a larger proportion of black and hispanic residents. Greater access to healthcare is associated with wealthier communities, which tend to have a larger proportion of white residents. IPD patients that seek care may be more likely to be diagnosed with septic shock. However, given the small sample analyzed in this model, these results should be taken with caution and repeated analysis should be performed in the future to determine the significance of these interactions.

Surprisingly, no ACIP noted underlying conditions were found to be significantly associated with death. Additionally, no individual pneumococcal vaccine was associated with mortality. This may have been an artifact of the small sample of cases analyzed from Period 3. Additional analysis should be done with more years of surveillance data to validate the strength of these findings.

Strengths & Limitations

This study had multiple strengths. First, the data examined in this analysis was collected via GAEIP's active-, laboratory-, population-based surveillance system over a ten year time frame. 1,457 elderly IPD cases were included. This large, population-based dataset provides a broad picture of IPD trends that can be used to direct future IPD prevention strategies in the elderly. Second, the surveillance area and cases in this analysis contained a high percentage of both black and white individuals allowing for race-specific rates to be examined. Third, risk-factors for mortality were examined in cases from the late PCV13 era, allowing for vaccination status to be considered as a potential exposure in the mortality model.

This study also had several limitations. First, the modeling portion of this study only examined 425 cases (including 75 deaths) – a relatively small sample size for analysis. Second, IPD mortality was modeled via logistic regression instead of a more robust method due to data limitations: 1) IPD culture date was not available for this analysis, so year of culture was used instead, 2) pneumococcal vaccine date was not available for this analysis, only pneumococcal vaccination type, and 3) other clinical variables of significance to IPD (such as influenza vaccination status and date of influenza infection) were not available for this analysis. If these data were available, a time-series analysis of IPD mortality would have been preferred to account for seasonal variability in IPD. Last, there are some notable limitations in generalizability of

results from this analysis: 1) this analysis focused on IPD only and results may not apply to non-invasive pneumococcal disease, and 2) this analysis was limited to residents of the greater Atlanta area and may not be representative of local epidemiology in other regions of United States.

Public Health Importance & Future Directions

This study provided an update on the epidemiology of IPD in older adults aged ≥65 years old, a population at increased risk for pneumococcal infections and mortality. Current vaccination programs and prevention strategies have led to significant reductions in IPD incidence in this population. In the Atlanta MSA, IPD incidence dropped beneath the target rate identified in the Healthy People 2020 goals for adults aged ≥65 years old (23.68 per 100,000 vs. target 31.0 per 100,000).[31]

Although target reductions in IPD incidence have been reached, the target for pneumococcal vaccine coverage has not been achieved. In the Atlanta MSA, vaccination coverage with any pneumococcal vaccine was far below the Healthy People 2020 target (43.7% vs. target 90%).[31] When broken down by race, blacks had an even lower coverage rate (38.6% in blacks vs. 49.3% in whites). In spite of these low vaccination rates, receipt of any pneumococcal vaccine was found to have a protective effect in preventing IPD-related mortality in the modeling portion of this analysis, suggesting that increased pneumococcal vaccination coverage has even greater potential to prevent future IPD-related death in elderly populations. Previous studies found that adding PCV13 to vaccination schedule at age 65 reduced IPD incidence and related deaths.[27, 51]

Recent analyses have indicated that the greatest impact of PCV13 vaccination in adults would occur with rapid uptake and improved vaccine coverage during the first three years post-

PCV13 introduction in adults.[24] As time goes on and pneumococcal vaccination coverage remains low in elderly populations, future pneumococcal vaccination recommendations must consider the cost-effectiveness and projected benefit of continued PCV13 vaccination in adults aged ≥65 years old. Continued surveillance in this population in upcoming years will be essential in making policy decisions on future pneumococcal vaccination practices and IPD prevention.

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APPENDIX

Tables

Table 1A. Demographic characteristics for adults ≥65 years old with IPD stratified by study period[a]: 20-county Atlanta MSA, Georgia, 2008-2017

Variables	Total (n=1,547)		Period 1[a] (n=539)		Period 2[a] (n=566)		Period 3[a] (n=442)	
	No.	%	No.	%	No.	%	No.	%
Gender								
Female	858	55.5	315	58.4	302	53.4	241	54.5
Male	687	44.4	224	41.6	264	46.6	199	45.0
Age, years								
65-74	748	48.4	256	47.5	266	47.0	226	51.1
75+	799	51.6	283	52.5	300	53.0	216	48.9
Median age, years (IQR range)	75 (69-82)		76 (69-84)		75 (69-82)		74 (69-81)	
Race								
White	1,099	71.0	411	76.3	402	71.0	286	65.0
Black or African American	392	25.3	110	20.4	149	26.3	133	30.2
Other	19	1.2	8	1.5	4	0.7	7	1.6
***S. pneumoniae* serotype**								
PCV7-Type[ŧ]	52	3.4	24	4.5	16	2.8	12	2.7
PCV13-Type[ł]	428	27.7	205	38.0	141	24.9	82	18.6
PPV11-Type[ŧ]	390	25.2	103	19.1	164	29.0	123	27.8
Non-Vaccine Type	493	31.9	137	25.4	184	32.5	172	38.9
Unknown[Ᵽ]	184	11.9	70	13.0	61	10.8	53	12.0

[a]Study periods were defined based on changing vaccination recommendations for *S. pneumoniae* by ACIP: Period 1=2008-2010, Period 2=2011-2014, Period 3=2015-2017.

[ŧ]PCV7-types include IPD serotypes 4, 6B, 9V, 14, 18C, 19F, 23F, and 6A

[ł]PCV13-types include IPD serotypes 19A, 7F, 5, 3, 1 and 6C

[ŧ]PPV11-types include IPD serotypes 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, and 33F

[Ᵽ]No isolate available for serotyping; serotype is unknown

Table 1B. Admission characteristics for adults ≥65 years old with IPD stratified by study period[a]: 20-county Atlanta MSA, Georgia, 2008-2017

Variables	Total (n=1,547)		Period 1[a] (n=539)		Period 2[a] (n=566)		Period 3[a] (n=442)	
	No.	%	No.	%	No.	%	No.	%
Hospitalized								
Yes	1,476	94.1	507	94.1	550	97.2	419	94.8
No	71	4.6	32	5.9	16	2.8	23	5.2
Median hospital stay, days (IQR range)	7 (4-11)		7 (4-11)		6 (4-11)		7 (4-12)	
Clinical manifestation of disease[b]								
Pneumonia	1,174	75.9	422	78.3	439	77.6	313	70.8
Septic Shock	199	12.9	35	6.5	78	13.8	86	19.5
Bacteremia	176	11.4	63	11.7	62	11.0	51	11.5
Meningitis	73	4.7	21	3.9	34	6.0	18	4.1
Empyema	37	2.4	16	3.0	9	1.6	12	2.7
Other[c]	154	10.0	33	6.1	72	12.7	49	11.1
Underlying disease[b]: ACIP indications for vaccination, n								
≥4	220	14.2	60	11.1	82	14.5	78	17.6
3	249	16.1	76	14.1	108	19.1	65	14.7
2	409	26.4	142	26.4	138	24.4	129	29.2
1	428	27.7	179	33.2	155	27.4	94	21.3
0	241	15.6	82	15.2	83	14.7	76	17.2
No underlying conditions	185	12.0	47	8.7	70	12.4	68	15.4
ICU admission[d]								
Yes	501	32.4	67	12.4	239	42.2	195	44.3
No	647	41.8	114	21.2	310	54.8	223	50.7
Unknown	399	25.8	358	66.4	17	3.0	24	5.5
Outcome								
Survived	1,301	84.1	458	85.0	492	86.9	351	79.8
Died	230	14.9	81	15.0	74	13.1	75	17.0

[a]Study periods were defined based on changing vaccination recommendations for *S. pneumoniae* by ACIP: Period 1=2008-2010, Period 2=2011-2014, Period 3=2015-2017.
[b]Cases may have more than one clinical syndrome or underlying condition (disease data includes all conditions that apply).
[c]Most common other syndrome listed was Pleural effusion, accounting for 83/185 cases with other IPD syndrome. (Pleural effusion is not a valid infection type per CDC ABCs Core Surveillance instructions).
[d]ICU data available for 2010-2017 only.

Table 2. Presence of underlying disease defined as ACIP indications for pneumococcal vaccination among IPD cases ≥65 years old in Atlanta's 20-county MSA, stratified by study period[a]

Underlying Disease	Total (n=1,547)		Period 1[a] (n=539)		Period 2[a] (n=566)		Period 3[a] (n=442)	
	No.	%	No.	%	No.	%	No.	%
AIDS	5	0.3	1	0.2	4	0.7	0	0.0
Asthma	135	8.7	40	7.4	61	10.8	34	7.7
ASCVD/CAD	396	25.6	146	27.1	145	25.6	105	23.8
Bone marrow transplant	4	0.3	1	0.2	1	0.2	2	0.5
Chronic kidney disease[b]	189	18.8	0	0.0	100	17.7	89	20.1
Chronic liver disease/cirrhosis	37	2.4	16	3.0	6	1.1	15	3.4
Current chronic dialysis[c]	74	4.8	45	8.4	20	3.5	9	2.4
Cochlear implant	1	0.1	0	0.0	1	0.2	0	0.0
Complement deficiency	0	0.0	0	0.0	0	0.0	0	0.0
CSF leak	3	0.2	1	0.2	2	0.4	0	0.0
Diabetes	469	30.3	137	25.4	194	34.3	138	31.2
Emphysema/COPD	513	33.2	185	34.3	179	31.6	149	33.7
Heart Failure/CHF	353	22.8	133	24.7	121	21.4	99	22.4
HIV	9	0.6	3	0.6	4	0.7	2	0.5
Hodgkin's disease/lymphoma	36	2.3	14	2.6	14	2.5	8	1.8
Immunoglobulin deficiency	5	0.3	4	0.7	0	0.0	1	0.2
Immunosuppressive therapy	172	11.1	66	12.2	59	10.4	47	10.6
Leukemia	55	3.6	17	3.2	22	3.9	16	3.6
Multiple Myeloma	70	4.5	24	4.5	24	4.2	22	5.0
Nephrotic syndrome	2	0.1	2	0.4	0	0.0	0	0.0
Obesity	114	7.4	31	5.8	40	7.1	43	9.7
Sickle cell disease	0	0.0	0	0.0	0	0.0	0	0.0
Solid organ malignancy	285	18.4	83	15.4	109	19.3	93	21.0
Solid organ transplant	13	0.8	5	0.9	4	0.7	4	0.9
Splenectomy/Asplenia	24	1.6	8	1.5	9	1.6	7	1.6
Current smoker/Tobacco abuse	269	17.4	89	16.5	83	14.7	97	22.0
Current alcohol abuse	25	3.4	0	0.00	11	3.7	14	3.2
No underlying conditions	185	12.0	47	8.7	70	12.4	68	15.4

[a]Study periods were defined based on changing vaccination recommendations for *S. pneumoniae* by ACIP: Period 1=2008-2010, Period 2=2011-2014, Period 3=2015-2017.

[b]Chronic kidney disease was collected from 2014-2017 only. Chronic renal insufficiency was previously collected from 2011-2013 only.

[c]Current chronic dialysis was collected from 2014-2017 only. History of any dialysis (regardless of chronicity) was collected from 2008-2013.

Table 3. Vaccination status of IPD cases ≥65 years old in Atlanta's 20-county MSA, stratified by study period[a]

Variables	Total (n=1,008)		Period 2[a] (n=566)		Period 3[a] (n=442)	
	No.	%	No.	%	No.	%
Vaccination status[b‡]						
Yes	437	43.4	244	43.1	193	43.7
No	267	26.5	136	24.0	131	29.6
Unknown	304	30.2	186	32.9	118	26.7
Type of vaccine received						
PCV7 only	2	0.2	1	0.2	1	0.2
PCV13 only	21	2.1	0	0.0	21	4.8
PPSV23 only	232	23.0	114	20.1	118	26.7
PCV13 & PPSV23	19	1.9	0	0.0	19	4.3
Vaccine type not specified	163	16.2	129	22.8	34	7.7
Missing	304	30.2	186	32.9	118	26.7
None	267	26.5	136	24.0	131	29.6

[a]Study periods were defined based on changing vaccination recommendations for *S. pneumoniae* by ACIP: Period 1=2008-2010, Period 2=2011-2014, Period 3=2015-2017.
[b]Vaccine data available for 2011-2017 only. Cases from Period 1 (2008-2010) are excluded from this table.
‡Patients may have received more than one pneumococcal vaccine.

Table 4A. Incidence[a] of IPD among adults ≥65 years old stratified by gender, race, age and serotype: 20-county Atlanta MSA, Georgia, 2008-2012

	2008		2009		2010		2011		2012	
Variable	**N**	**Inc[a]**	**N**	**Inc[a]**	**N**	**Inc[a]**	**N**	**Inc[a]**	**N**	**Inc[a]**
Overall	156	37.53	194	44.56	189	41.99	122	25.59	147	28.70
Gender										
Male	74	42.45	74	40.41	76	39.90	50	24.65	70	31.98
Female	82	33.97	120	47.58	113	43.52	72	26.29	77	26.25
Age, years										
65-74	77	31.56	93	35.92	86	31.86	48	16.66	76	24.01
75+	79	46.01	101	57.23	103	57.15	74	39.26	71	36.28
Race										
White	124	39.78	147	45.62	140	42.27	91	26.15	110	29.50
Black or African American	25	27.89	42	43.11	43	42.20	30	27.36	32	27.02
***S. pneumoniae* serotype[b]**										
PCV7-Type[ŧ]	6	1.44	11	2.53	7	1.56	4	0.84	2	0.39
PCV13-Type[ł]	47	11.31	82	18.84	76	16.88	36	7.55	50	9.76
PPV11-Type[ŧ]	36	8.66	27	6.20	40	8.89	37	7.76	35	6.83
Non-Vaccine Type	44	10.58	45	10.34	48	10.66	26	5.45	43	8.39

[a]Incidence rates represent the average annual incidence per 100,000 population

[b]184 cases without an isolate available for serotyping were excluded from serotype analysis.

[ŧ]PCV7-types include IPD serotypes 4, 6B, 9V, 14, 18C, 19F, 23F, and 6A

[ł]PCV13-types include IPD serotypes 19A, 7F, 5, 3, 1 and 6C

[ŧ]PPV11-types include IPD serotypes 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, and 33F

Table 4B. Incidence[a] of IPD among adults ≥65 years old stratified by gender, race, age and serotype: 20-county Atlanta MSA, Georgia, 2013-2017

	2013		2014		2015		2016		2017	
Variable	**N**	**Inc[a]**	**N**	**Inc[a]**	**N**	**Inc[a]**	**N**	**Inc[a]**	**N**	**Inc[a]**
Overall	159	29.18	138	23.92	142	23.39	142	22.27	158	23.68
Gender										
Male	79	33.77	65	26.20	71	27.15	64	23.32	64	22.24
Female	80	25.73	73	22.20	71	20.55	78	21.48	92	24.25
Age, years										
65-74	70	20.53	72	19.77	71	18.44	70	17.24	85	19.98
75+	89	43.66	66	31.01	71	31.98	72	31.08	73	30.21
Race										
White	115	29.30	86	20.95	89	20.86	97	21.91	100	21.87
Black or African American	41	31.68	46	32.66	49	32.15	39	23.67	45	25.45
***S. pneumoniae* serotype[b]**										
PCV7-Type[ŧ]	4	0.73	6	1.04	3	0.49	6	0.94	3	0.45
PCV13-Type[ł]	30	5.51	25	4.33	20	3.29	15	2.35	47	7.04
PPV11-Type[ŧ]	55	10.09	37	6.41	37	6.10	42	6.59	44	6.60
Non-Vaccine Type	58	10.64	57	9.88	63	10.38	58	9.10	51	7.64
Missing	12	2.20	13	2.25	19	3.13	21	3.29	13	1.95

[a]Incidence rates represent the average annual incidence per 100,000 population

[b]184 cases without an isolate available for serotyping were excluded from serotype analysis.

[ŧ]PCV7-types include IPD serotypes 4, 6B, 9V, 14, 18C, 19F, 23F, and 6A

[ł]PCV13-types include IPD serotypes 19A, 7F, 5, 3, 1 and 6C

[ŧ]PPV11-types include IPD serotypes 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, and 33F

Table 4C. Incidence rate[a] and rate ratio[b] of IPD among adults ≥65 years old, stratified by gender, race, age and serotype: 20-county Atlanta MSA, Georgia, 2008-2017

	Period 1[c]			Period 2[c]			Period 3[c]			All years			
Variable	**N**	**Inc[a]**	**RR[b]**	**N**	**Inc[a]**	**RR[b]**	**N**	**Inc[a]**	**RR[b]**	**N**	**Inc[a]**	**RR[b]**	**P-Value**
Overall	539	41.42	--	566	26.81	--	442	23.12	--	1547	29.06	--	**0.0007***
Gender													
Male	224	40.88	ref	264	29.21	ref	199	24.16	ref	687	30.19	ref	0.3001
Female	315	41.82	1.02	302	25.02	0.86	241	22.15	0.92	858	28.15	0.93	0.2621
Age, years													
65-74	256	33.13	ref	266	20.31	ref	226	18.58	ref	748	22.67	ref	0.4016
75+	283	53.56	1.62	300	37.46	1.84	216	31.07	1.67	799	39.47	1.74	0.4016
Race													
White	411	42.59	ref	402	26.38	ref	286	21.56	ref	1,099	28.80	ref	**0.0026***
Black or African American	110	38.07	0.89	149	29.90	1.13	133	26.93	1.25	392	30.60	1.06	**0.0077***
***S. pneumoniae* serotype[d]**													
PCV7-Type[ŧ]	24	1.84	0.18	16	0.76	0.09	12	0.63	0.07	52	0.98	0.11	0.1721
PCV13-Type[ŧ]	205	15.75	1.50	141	6.68	0.77	82	4.29	0.48	428	8.04	0.87	**<0.0001***
PPV11-Type[ŧ]	103	7.92	0.75	164	7.77	0.89	123	6.43	0.72	390	7.33	0.79	**0.0016***
Non-Vaccine Type	137	10.53	ref	184	8.72	ref	172	9.00	ref	493	9.26	ref	**<0.0001***

*Statistically significant (p<0.05) by Pearson's chi-squared test.

[a]Incidence rates represent the average period incidence per 100,000 population.

[b]Rate ratios represent the ratio of the incidence rate in a group to the incidence rate in the reference group.

[c]Study periods were defined based on changing vaccination recommendations for *S. pneumoniae* by ACIP: Period 1=2008-2010, Period 2=2011-2014, Period 3=2015-2017.

[d]184 cases without an isolate available for serotyping were excluded from serotype analysis.

[ŧ]PCV7-types include IPD serotypes 4, 6B, 9V, 14, 18C, 19F, 23F, and 6A

[ŧ]PCV13-types include IPD serotypes 19A, 7F, 5, 3, 1 and 6C

[ŧ]PPV11-types include IPD serotypes 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, and 33F

Table 5A. Incidence[a] of IPD among adults ≥65 years old, race stratified by age and serotype: 20-county Atlanta MSA, Georgia, 2008-2012

Variable			2008		2009		2010		2011		2012	
			N	Inc[a]	N	Inc[a]	N	Inc[a]	N	Inc[a]	N	Inc[a]
Overall			156	37.53	194	44.56	189	41.99	122	25.59	147	28.70
Race	White	All whites	124	39.78	147	45.62	140	42.27	91	26.15	110	29.50
		Male	56	41.93	57	41.01	63	43.81	42	27.63	54	32.98
		Female	68	38.17	90	49.12	77	41.10	49	25.00	56	26.78
		65-74	57	32.35	70	37.80	62	32.28	34	16.67	54	24.06
		75+	67	49.44	77	56.18	78	56.08	57	39.58	56	37.73
		Male, 65-74	29	35.05	29	33.32	34	37.56	19	19.73	32	30.20
		Female, 65-74	28	29.96	41	41.78	28	27.57	15	13.93	22	18.57
		Male, 75+	27	53.13	28	53.92	29	54.43	23	41.30	22	38.09
		Female, 75+	40	47.22	49	57.57	49	57.10	34	38.50	34	37.51
	Black or African American	All blacks	25	27.89	42	43.11	43	42.20	30	27.36	32	27.02
		Male	15	44.05	14	38.05	9	23.25	8	19.07	12	26.41
		Female	10	17.99	28	46.18	34	53.80	22	32.48	20	27.41
		65-74	17	29.41	21	33.47	21	31.81	14	19.68	19	24.43
		75+	8	25.15	21	60.57	22	61.30	16	41.54	13	31.98
		Male, 65-74	8	33.33	4	15.43	4	14.61	5	16.89	7	21.69
		Female, 65-74	9	26.62	17	46.17	17	43.99	9	21.66	12	26.38
		Male, 75+	7	69.69	10	92.08	5	44.13	3	24.30	5	38.01
		Female, 75+	1	4.59	11	46.20	17	69.23	13	49.68	8	29.10

[a]Incidence rates represent the average annual incidence per 100,000 population

Table 5B. Incidence of IPD among adults ≥65 years old, race stratified by age and serotype: 20-county Atlanta MSA, Georgia, 2013-2017

Variable			2013		2014		2015		2016		2017	
			N	Inc[a]	N	Inc[a]	N	Inc[a]	N	Inc[a]	N	Inc[a]
Overall			159	29.18	138	23.92	142	23.39	142	22.27	158	23.68
Race	White	All whites	115	29.30	86	20.95	89	20.86	97	21.91	100	21.87
		Male	59	34.05	47	25.89	48	25.39	45	22.95	47	23.13
		Female	56	25.55	39	17.03	41	17.25	52	21.08	53	20.87
		65-74	51	21.28	42	16.61	41	15.54	43	15.68	50	17.67
		75+	64	41.90	44	27.90	48	29.47	54	32.04	50	28.69
		Male, 65-74	29	25.66	22	18.52	25	20.19	20	15.63	27	20.50
		Female, 65-74	22	17.36	20	14.92	16	11.42	23	15.73	23	15.21
		Male, 75+	30	49.79	25	39.85	23	35.24	25	36.72	20	27.95
		Female, 75+	34	36.76	19	20.00	25	25.62	29	28.87	30	29.21
	Black or African American	All blacks	41	31.68	46	32.66	49	32.15	39	23.67	45	25.45
		Male	17	33.99	15	27.43	21	35.40	17	26.46	12	17.29
		Female	24	30.23	31	35.98	28	30.08	22	21.89	33	30.72
		65-74	18	20.99	28	29.75	29	28.30	23	20.57	27	22.36
		75+	23	52.67	18	38.51	20	40.06	16	30.23	18	32.11
		Male, 65-74	11	30.89	8	20.51	16	37.79	9	19.59	8	16.15
		Female, 65-74	7	13.96	20	36.30	13	21.62	14	21.25	19	26.68
		Male, 75+	6	41.68	7	44.65	5	29.46	8	43.70	4	20.14
		Female, 75+	17	58.08	11	35.41	15	45.52	8	23.11	14	38.67

[a]Incidence rates represent the average annual incidence per 100,000 population

Table 5C. Incidence rate[a] and rate ratio[b] of IPD among adults ≥65 years old, race stratified by age and serotype: 20-county Atlanta MSA, Georgia, 2008-2017

Variable			Period 1[c]			Period 2[c]			Period 3[c]			All years			
			N	Inc[a]	RR[b]	N	Inc[a]	RR[b]	N	Inc[a]	RR[b]	N	Inc[a]	RR[b]	P-Value
Overall			539	41.4	--	566	26.8	--	442	23.1	--	1547	29.1	--	**0.0007***
Race	White	All whites	411	42.6	ref	402	26.4	ref	286	21.6	Ref	1099	28.8	ref	**0.0026***
		Male	176	42.3	0.99	202	30.1	1.14	140	23.8	1.10	518	32.5	1.13	0.5114
		Female	235	42.8	1.01	200	23.4	0.89	146	19.8	0.92	581	27.1	0.94	**0.0014***
		65-74	189	34.2	0.80	181	19.7	0.75	134	16.3	0.76	504	22.0	0.76	0.0595
		75+	222	53.9	1.27	221	36.7	1.39	152	30.1	1.39	595	39.1	1.36	0.2599
		Male, 65-74	92	35.3	0.83	102	23.5	0.89	72	18.8	0.87	266	24.7	0.86	0.3228
		Female, 65-74	97	33.1	0.78	79	16.2	0.62	62	14.2	0.66	238	19.5	0.68	0.1728
		Male, 75+	84	53.8	1.26	100	42.3	1.60	68	33.2	1.54	252	42.2	1.46	0.9382
		Female, 75+	138	54.0	1.27	121	33.0	1.25	84	27.9	1.30	343	37.2	1.29	**0.0253***
	Black or African American	All blacks	110	38.1	ref	149	29.9	ref	133	26.9	Ref	392	30.6	ref	**0.0077***
		Male	38	34.7	0.91	52	27.1	0.91	50	25.9	0.96	140	28.3	0.93	0.3326
		Female	72	40.1	1.05	97	31.7	1.06	83	27.6	1.02	252	32.0	1.05	**0.0023***
		65-74	59	31.6	0.83	79	24.0	0.80	79	23.6	0.88	217	25.5	0.83	0.1036
		75+	51	49.8	1.31	70	41.3	1.38	54	34.0	1.26	175	40.6	1.33	0.2817
		Male, 65-74	16	20.7	0.54	31	22.7	0.76	33	23.9	0.89	80	22.8	0.74	0.0992
		Female, 65-74	43	39.4	1.03	48	25.0	0.83	46	23.3	0.87	137	27.5	0.90	0.3399
		Male, 75+	22	68.2	1.79	21	37.8	1.26	17	30.8	1.14	60	42.0	1.37	0.9296
		Female, 75+	29	41.3	1.09	49	43.0	1.44	37	35.7	1.32	115	39.9	1.31	**0.0087***

*Statistically significant (p<0.05) by Pearson's chi-squared test.

[a]Incidence rates represent the average period incidence per 100,000 population.

[b]Rate ratios represent the ratio of the incidence rate in a group to the incidence rate in the reference group.

[c]Study periods were defined based on changing vaccination recommendations for *S. pneumoniae* by ACIP: Period 1=2008-2010, Period 2=2011-2014, Period 3=2015-2017.

Table 6A. Incidence rate[a] of IPD among adults ≥65 years old stratified by serotype group and serotype: 20-county Atlanta MSA, Georgia, 2008-2012.

S. pneumoniae serotype[b]		2008		2009		2010		2011		2012	
		N	Inc[a]	N	Inc[a]	N	Inc[a]	N	Inc[a]	N	Inc[a]
Overall		156	37.53	194	44.56	189	41.99	122	25.59	147	28.70
PCV7-Type[Ł]	All PCV7	6	1.44	11	2.53	7	1.56	4	0.84	2	0.39
	4	0	0.00	0	0.00	1	0.22	1	0.21	0	0.00
	6B	1	0.24	1	0.23	0	0.00	0	0.00	0	0.00
	6A	2	0.48	4	0.92	0	0.00	0	0.00	0	0.00
	9V	2	0.48	2	0.46	1	0.22	1	0.21	0	0.00
	14	0	0.00	0	0.00	2	0.44	0	0.00	1	0.20
	18C	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
	19F	1	0.24	3	0.69	3	0.67	2	0.42	1	0.20
	23F	0	0.00	1	0.23	0	0.00	0	0.00	0	0.00
PCV13-Type[ł]	All PCV13	47	11.31	82	18.84	76	16.88	36	7.55	50	9.76
	1	0	0.00	0	0.00	0	0.00	1	0.21	0	0.00
	3	6	1.44	12	2.76	19	4.22	8	1.68	21	4.10
	5	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
	6C	13	3.13	12	2.76	16	3.55	10	2.10	12	2.34
	7F	12	2.89	28	6.43	18	4.00	6	1.26	8	1.56
	19A	16	3.85	30	6.89	23	5.11	11	2.31	9	1.76
PPV11-Type[Ł]	All PPV11	36	8.66	27	6.20	40	8.89	37	7.76	35	6.83
	2	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
	8	2	0.48	0	0.00	1	0.22	0	0.00	0	0.00
	9N	1	0.24	3	0.69	8	1.78	1	0.21	4	0.78
	10A	0	0.00	2	0.46	1	0.22	1	0.21	0	0.00
	11A	8	1.92	6	1.38	6	1.33	2	0.42	7	1.37
	12F	0	0.00	2	0.46	4	0.89	5	1.05	4	0.78
	15B	2	0.48	0	0.00	0	0.00	3	0.63	3	0.59
	17F	2	0.48	0	0.00	1	0.22	3	0.63	0	0.00
	20	1	0.24	0	0.00	2	0.44	0	0.00	2	0.39
	22F	10	2.41	11	2.53	14	3.11	17	3.57	11	2.15
	33F	10	2.41	3	0.69	3	0.67	5	1.05	4	0.78
Non-Vaccine Type		44	10.58	45	10.34	48	10.66	26	5.45	43	8.39

[a]Incidence rates represent the average annual incidence per 100,000 population

[b]184 cases without an isolate available for serotyping were excluded from serotype analysis.

[Ł]PCV7-types include IPD serotypes 4, 6B, 9V, 14, 18C, 19F, 23F, and 6A

[ł]PCV13-types include IPD serotypes 19A, 7F, 5, 3, 1 and 6C

[Ł]PPV11-types include IPD serotypes 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, and 33F

Table 6B. Incidence rate[a] of IPD among adults ≥65 years old stratified by serotype group and serotype: 20-county Atlanta MSA, Georgia, 2013-2017

S. pneumoniae serotype[b]		2013		2014		2015		2016		2017	
		N	Inc[a]	N	Inc[a]	N	Inc[a]	N	Inc[a]	N	Inc[a]
Overall		159	29.18	138	23.92	142	23.39	142	22.27	158	23.68
PCV7-Type[Ł]	All PCV7	4	0.73	6	1.04	3	0.49	6	0.94	3	0.45
	4	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
	6B	1	0.18	1	0.17	1	0.16	1	0.16	1	0.15
	6A	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
	9V	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
	14	0	0.00	0	0.00	0	0.00	1	0.16	0	0.00
	18C	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
	19F	3	0.55	5	0.87	2	0.33	4	0.63	2	0.30
	23F	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
PCV13-Type[ł]	All PCV13	30	5.51	25	4.33	20	3.29	15	2.35	47	7.04
	1	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
	3	10	1.84	9	1.56	10	1.65	10	1.57	34	5.10
	5	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
	6C	9	1.65	12	2.08	7	1.15	1	0.16	5	0.75
	7F	3	0.55	2	0.35	1	0.16	0	0.00	0	0.00
	19A	8	1.47	2	0.35	2	0.33	4	0.63	8	1.20
PPV11-Type[Ł]	All PPV11	55	10.09	37	6.41	37	6.10	42	6.59	44	6.60
	2	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
	8	1	0.18	2	0.35	0	0.00	2	0.31	0	0.00
	9N	3	0.55	3	0.52	3	0.49	6	0.94	4	0.60
	10A	2	0.37	3	0.52	1	0.16	1	0.16	4	0.60
	11A	4	0.73	7	1.21	4	0.66	3	0.47	8	1.20
	12F	12	2.20	5	0.87	9	1.48	7	1.10	4	0.60
	15B	2	0.37	4	0.69	2	0.33	4	0.63	3	0.45
	17F	2	0.37	0	0.00	4	0.66	2	0.31	0	0.00
	20	1	0.18	2	0.35	3	0.49	1	0.16	4	0.60
	22F	24	4.40	10	1.73	7	1.15	14	2.20	12	1.80
	33F	4	0.73	1	0.17	4	0.66	2	0.31	5	0.75
Non-Vaccine Type		58	10.64	57	9.88	63	10.38	58	9.10	51	7.64

[a]Incidence rates represent the average annual incidence per 100,000 population

[b]184 cases without an isolate available for serotyping were excluded from serotype analysis.

[Ł]PCV7-types include IPD serotypes 4, 6B, 9V, 14, 18C, 19F, 23F, and 6A

[ł]PCV13-types include IPD serotypes 19A, 7F, 5, 3, 1 and 6C

[Ł]PPV11-types include IPD serotypes 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, and 33F

Table 7A. Incidence rate[a] of IPD among adults ≥65 years old stratified by serotype group and age: 20-county Atlanta MSA, Georgia, 2008-2012.

S. pneumoniae serotype[b]		2008		2009		2010		2011		2012	
		N	Inc[a]	N	Inc[a]	N	Inc[a]	N	Inc[a]	N	Inc[a]
Overall		156	37.53	194	44.56	189	41.99	122	25.59	147	28.70
PCV7-Type[ŧ]	All PCV7	6	1.44	11	2.53	7	1.56	4	0.84	2	0.39
	65-74	1	0.41	6	2.32	2	0.74	2	0.69	1	0.32
	75+	5	2.91	5	2.83	5	2.77	2	1.06	1	0.51
PCV13-Type[ŧ]	All PCV13	47	11.31	82	18.84	76	16.88	36	7.55	50	9.76
	65-74	25	10.25	43	16.61	38	14.08	13	4.51	23	7.27
	75+	22	12.81	39	22.10	38	21.09	23	12.20	27	13.80
PPV11-Type[ŧ]	All PPV11	36	8.66	27	6.20	40	8.89	37	7.76	35	6.83
	65-74	20	8.20	14	5.41	18	6.67	14	4.86	19	6.00
	75+	16	9.32	13	7.37	22	12.21	23	12.20	16	8.18
Non-Vaccine Type	All Non-VT	44	10.58	45	10.34	48	10.66	26	5.45	43	8.39
	65-74	21	8.61	18	6.95	22	8.15	11	3.82	22	6.95
	75+	23	13.40	27	15.30	26	14.43	15	7.96	21	10.73

[a]Incidence rates represent the average annual incidence per 100,000 population
[b]184 cases without an isolate available for serotyping were excluded from serotype analysis.
[ŧ]PCV7-types include IPD serotypes 4, 6B, 9V, 14, 18C, 19F, 23F, and 6A
[ł]PCV13-types include IPD serotypes 19A, 7F, 5, 3, 1 and 6C
[ŧ]PPV11-types include IPD serotypes 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, and 33F

Table 7B. Incidence rate[a] of IPD among adults ≥65 years old stratified by serotype group and age: 20-county Atlanta MSA, Georgia, 2013-2017.

S. pneumoniae serotype[b]		2013		2014		2015		2016		2017	
		N	Inc[a]	N	Inc[a]	N	Inc[a]	N	Inc[a]	N	Inc[a]
Overall		159	29.18	138	23.92	142	23.39	142	22.27	158	23.68
PCV7-Type[ŧ]	All PCV7	4	0.73	6	1.04	3	0.49	6	0.94	3	0.45
	65-74	3	0.88	3	0.82	2	0.52	3	0.74	3	0.71
	75+	1	0.49	3	1.41	1	0.45	3	1.30	0	0.00
PCV13-Type[ł]	All PCV13	30	5.51	25	4.33	20	3.29	15	2.35	47	7.04
	65-74	13	3.81	14	3.84	9	2.34	6	1.48	27	6.35
	75+	17	8.34	11	5.17	11	4.95	9	3.89	20	8.28
PPV11-Type[ŧ]	All PPV11	55	10.09	37	6.41	37	6.10	42	6.59	44	6.60
	65-74	23	6.74	19	5.22	21	5.45	24	5.91	18	4.23
	75+	32	15.70	18	8.46	16	7.21	18	7.77	26	10.76
Non-Vaccine Type	All Non-VT	58	10.64	57	9.88	63	10.38	58	9.10	51	7.64
	65-74	25	7.33	31	8.51	30	7.79	29	7.14	27	6.35
	75+	33	16.19	26	12.22	33	14.86	29	12.52	24	9.93

[a]Incidence rates represent the average annual incidence per 100,000 population
[b]184 cases without an isolate available for serotyping were excluded from serotype analysis.
[ŧ]PCV7-types include IPD serotypes 4, 6B, 9V, 14, 18C, 19F, 23F, and 6A
[ł]PCV13-types include IPD serotypes 19A, 7F, 5, 3, 1 and 6C
[ŧ]PPV11-types include IPD serotypes 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, and 33F

Table 7C. Incidence rate[a] and rate ratio[b] of IPD among adults ≥65 years old stratified by serotype group and age: 20-county Atlanta MSA, Georgia, 2008-2017

S. pneumoniae serotype[d]		Period 1[c]			Period 2[c]			Period 3[c]			All years			
		N	Inc[a]	RR[b]	N	Inc[a]	RR[b]	N	Inc[a]	RR[b]	N	Inc[a]	RR[b]	P-Value
Overall		539	41.4	--	566	26.8	--	442	23.1	--	1547	29.1	--	**0.0007***
PCV7-Type[ŧ]	All PCV7	24	1.84	ref	16	0.76	ref	12	0.63	ref	52	0.98	ref	0.1721
	65-74	9	1.16	0.631	9	0.69	0.906	8	0.66	1.048	26	0.79	0.81	0.8555
	75+	15	2.84	1.539	7	0.87	1.153	4	0.58	0.917	26	1.28	1.31	**0.0308***
PCV13-Type[ŧ]	All PCV13	205	15.75	ref	141	6.68	ref	82	4.29	ref	428	8.04	ref	**<0.0001***
	65-74	106	13.72	0.871	63	4.81	0.72	42	3.45	0.805	211	6.40	0.80	**<0.0001***
	75+	99	18.74	1.189	78	9.74	1.458	40	5.75	1.341	217	10.72	1.33	**<0.0001***
PPV11-Type[ŧ]	All PPV11	103	7.92	ref	164	7.77	ref	123	6.43	ref	390	7.33	ref	**0.0016***
	65-74	52	6.73	0.850	75	5.73	0.737	63	5.18	0.805	190	5.76	0.786	0.1625
	75+	51	9.65	1.219	89	11.11	1.43	60	8.63	1.341	200	9.88	1.348	**0.0096***
Non-Vaccine Type	All Non-VT	137	10.53	ref	184	8.72	ref	172	9.00	ref	493	9.26	ref	**<0.0001***
	65-74	61	7.89	0.75	89	6.79	0.779	86	7.07	0.786	236	7.15	0.772	**0.0080***
	75+	76	14.38	1.366	95	11.86	1.361	86	12.37	1.375	257	12.69	1.371	**0.0156***

*Statistically significant (p<0.05) by Pearson's chi-squared test.

[a]Incidence rates represent the average period incidence per 100,000 population.

[b]Rate ratios represent the ratio of the incidence rate in a group to the incidence rate in the reference group.

[c]Study periods were defined based on changing vaccination recommendations for *S. pneumoniae* by ACIP: Period 1=2008-2010, Period 2=2011-2014, Period 3=2015-2017.

[d]184 cases without an isolate available for serotyping were excluded from serotype analysis.

[ŧ]PCV7-types include IPD serotypes 4, 6B, 9V, 14, 18C, 19F, 23F, and 6A

[ŧ]PCV13-types include IPD serotypes 19A, 7F, 5, 3, 1 and 6C

[ŧ]PPV11-types include IPD serotypes 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, and 33F

Table 8A. Mortality model variable selection for IPD cases in adults ≥65 years old stratified by patient outcome in period 3[a] in Atlanta's 20-county MSA.

Variable	Invasive *S. pneumoniae* Cases (2015-2017) Fraction Survived (%)	Fraction Died (%)	RelRisk	95% CI		P-Value
Gender						
Male	152/193 (78.76)	41/193 (21.24)	0.79	0.62	1.00	0.073
Age, years						
65-74	175/216 (81.02)	41/216 (18.98)	0.91	0.72	1.15	0.449
75+	176/210 (83.81)	34/210 (16.19)	1.11	0.84	1.44	0.449
Race						
White	228/280 (81.43)	52/280 (18.57)	0.94	0.79	1.11	0.467
Black or African American	**116/132 (87.88)**	**16/132 (12.12)**	**1.55**	**0.98**	**2.45**	**0.046***
Hospitalization						
Hospitalized	344/418 (82.30)	74/418 (17.70)	0.99	0.96	1.02	0.702
ICU admission	**135/194 (69.59)**	**59/194 (30.41)**	**0.49**	**0.41**	**0.59**	**<0.0001***
Vaccination Status						
PCV13 only	20/21 (95.24)	1/21 (4.76)	4.27	0.58	31.35	0.146[∂]
PPV23 only	98/118 (83.05)	20/118 (16.95)	1.05	0.69	1.58	0.826
PCV13 & PPV23	17/19 (89.47)	2/19 (10.53)	1.82	0.43	7.69	0.548[∂]
Any pneumococcal vaccine	**166/192 (86.46)**	**26/192 (13.54)**	**1.36**	**0.98**	**1.90**	**0.046***
No pneumococcal vaccine	**185/234 (79.06)**	**49/234 (20.94)**	**0.81**	**0.67**	**0.98**	**0.046***
Clinical manifestation of disease[b]						
Pneumonia	262/312 (83.97)	50/312 (16.03)	1.12	0.94	1.33	0.157
Septic Shock	**55/86 (63.95)**	**31/86 (36.05)**	**0.38**	**0.26**	**0.54**	**<0.0001***
Bacteremia	42/51 (82.35)	9/51 (17.65)	1.00	0.51	1.96	0.993
Meningitis	15/18 (83.33)	3/18 (16.67)	1.07	0.32	3.60	1.0[∂]
Peritonitis	1/2 (50.00)	1/2 (50.00)	0.21	0.01	3.38	0.322[Δ]
Empyema	10/12 (83.33)	2/12 (16.67)	1.07	0.24	4.78	0.931
Other syndrome[c]	39/49 (79.59)	10/49 (20.41)	0.83	0.44	1.59	0.584

*Statistically significant (p<0.05) by Pearson's chi-squared test.
[Δ]Chi-square test expected values less than <5 in 50% of cells. Fisher's exact test used instead.
[∂]Chi-square test expected values less than <5 in 25% of cells. Fisher's exact test used instead.
[a]Study periods were defined based on changing vaccination recommendations for *S. pneumoniae* by ACIP.
[b]Cases may have more than one clinical syndrome or underlying condition (disease data includes all conditions that apply).
[c]Most common other syndrome listed was Pleural effusion, accounting for 27/34 cases. (Pleural effusion is not a valid infection type per CDC ABCs Core Surveillance instructions).

Table 8B. Mortality model variable selection (continued) for IPD cases in adults ≥65 years old stratified by patient outcome in period 3[a] in Atlanta's 20-county MSA.

Variable	Invasive *S. pneumoniae* Cases (2015-2017) Fraction Survived (%)	Fraction Died (%)	RelRisk	95% CI		P-Value
Underlying disease[b]: ACIP indications for vaccination, n						
Asthma	29/34 (85.29)	5/34 (14.71)	1.24	0.50	3.10	0.644
ASCVD/CAD	86/105 (81.90)	19/105 (18.10)	0.97	0.63	1.49	0.879
Bone marrow transplant	1/2 (50.00)	1/2 (50.00)	0.21	0.01	3.38	0.322[Δ]
Chronic kidney disease[d]	76/89 (85.39)	13/89 (14.61)	1.24	0.73	2.13	0.404
Chronic liver disease/cirrhosis	12/15 (80.00)	3/15 (20.00)	0.85	0.25	2.95	0.735[∂]
Chronic heart disease[e]	133/164 (81.10)	31/164 (18.90)	0.92	0.68	1.24	0.578
Current chronic dialysis[f]	8/9 (88.89)	1/9 (11.11)	1.71	0.22	13.46	1.0[∂]
Diabetes	113/138 (81.88)	25/138 (18.12)	0.97	0.68	1.38	0.848
Emphysema/COPD	125/148 (84.46)	23/148 (15.54)	1.16	0.80	1.68	0.414
Heart Failure/CHF	78/99 (78.79)	21/99 (21.21)	0.79	0.53	1.2	0.282
Hodgkin's disease/lymphoma	6/8 (75.00)	2/8 (25.00)	0.64	0.13	3.11	0.635[∂]
Immunoglobulin deficiency	0/1 (0.00)	1/1 (100.00)	--	--	--	0.176[Δ]
Immunosupressive therapy	38/47 (80.85)	9/47 (19.15)	0.90	0.46	1.79	0.768
Leukemia	12/16 (75.00)	4/16 (25.00)	0.64	0.21	1.93	0.499[∂]
Multiple Myeloma	18/22 (81.82)	4/22 (18.18)	0.96	0.34	2.76	0.942
Obesity	34/43 (79.07)	9/43 (20.93)	0.81	0.40	1.61	0.546
Solid organ malignancy	76/93 (81.72)	17/93 (18.28)	0.96	0.60	1.52	0.847
Splenectomy/Asplenia	6/7 (85.71)	1/7 (14.29)	1.28	0.16	10.49	0.816[∂]
Current smoker/Tobacco abuse	78/96 (81.25)	18/96 (18.75)	0.93	0.59	1.45	0.738
Current alcohol abuse	12/14 (85.71)	2/14 (14.29)	1.28	0.29	5.61	1.0[∂]
No underlying conditions	45/53 (84.91)	8/53 (15.09)	1.20	0.59	2.44	0.608

*Statistically significant ($p<0.05$) by Pearson's chi-squared test.

[Δ]Chi-square test expected values less than <5 in 50% of cells. Fisher's exact test used instead.

[∂]Chi-square test expected values less than <5 in 25% of cells. Fisher's exact test used instead.

[a]Study periods were defined based on changing vaccination recommendations for *S. pneumoniae* by ACIP.

[b]Cases may have more than one clinical syndrome or underlying condition (disease data includes all conditions that apply).

[d]Chronic kidney disease variable collected from 2014-2017 (entire model time frame).

[e]Chronic heart disease is a combined variable of ASCVD and CHF.

[f]Current chronic dialysis variable collected from 2014-2017 (entire model time frame).

Table 9. Mortality model[z] values for adults ≥65 years old with IPD in period 3[a]: 20-county Atlanta MSA, Georgia, 2015-2017

Model term	β Estimate	P-Value	OR Estimate	95% CI	
Intercept (α)	-1.52	0.028	—	—	—
Any pneumonia shot	-0.70	0.018	0.50	0.28	0.89
Black race[b]	-2.09	0.004	0.19	0.05	0.76
White race	-0.51	0.457	—	—	—
ICU admission	1.58	<0.0001	4.85	2.48	9.48
Septic shock[c]	1.53	0.009	1.91	1.00	3.64
White race*Septic shock	-1.34	0.047	—	—	—
Current smoker	-0.43	0.274	—	—	—
Black race*Current smoker	1.91	0.016	—	—	—

[z]Goodness of fit=0.601
[a]Study periods were defined based on changing vaccination recommendations for *S. pneumoniae* by ACIP.
[b]Odds ratio and 95% confidence interval calculated holding current smoker at a constant (0.225) within the interaction term.
[c]Odds ratio and 95% confidence interval calculated holding white race at a constant (0.657) within the interaction term.

Figures

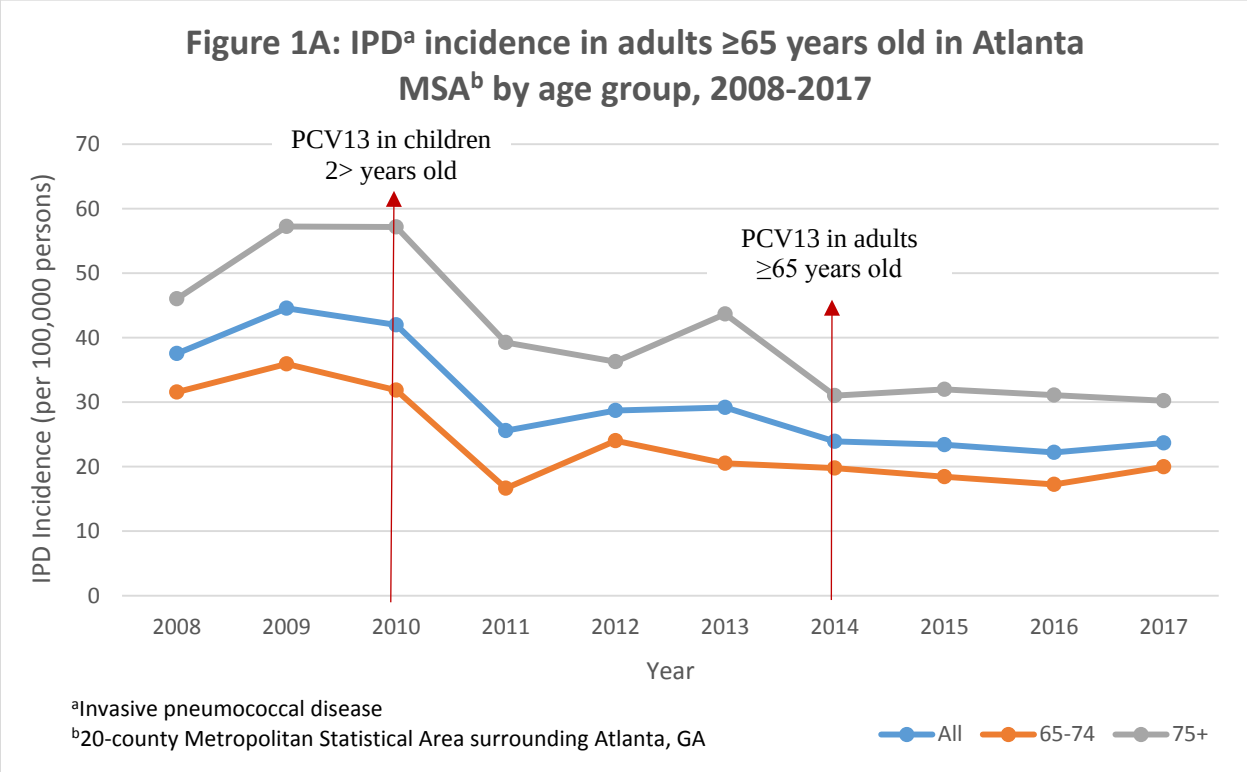
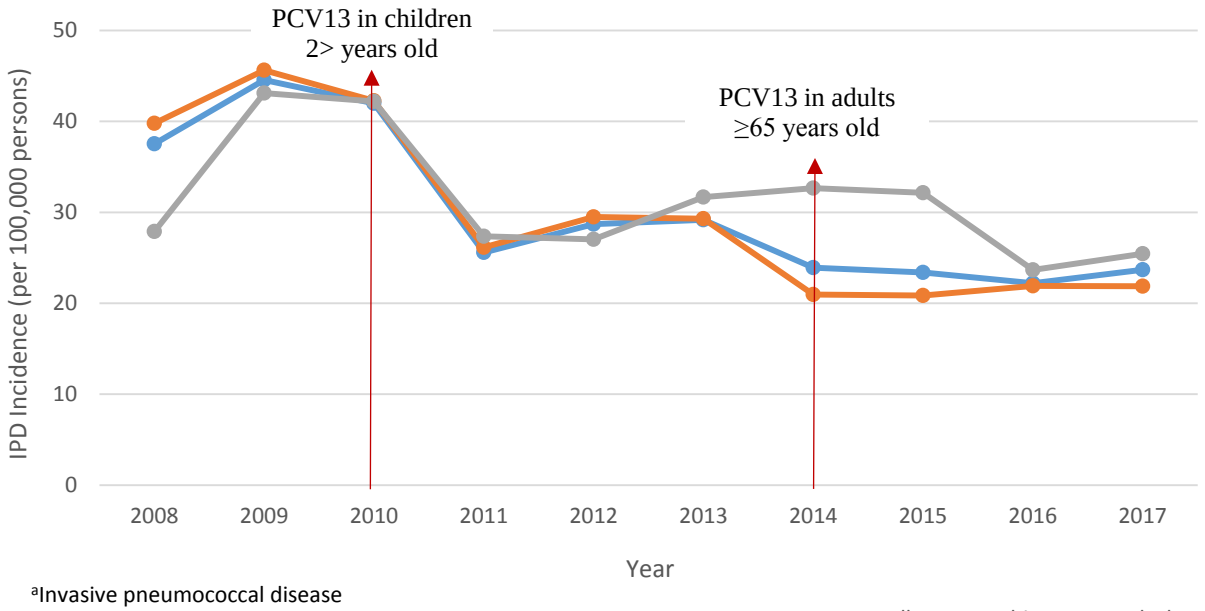
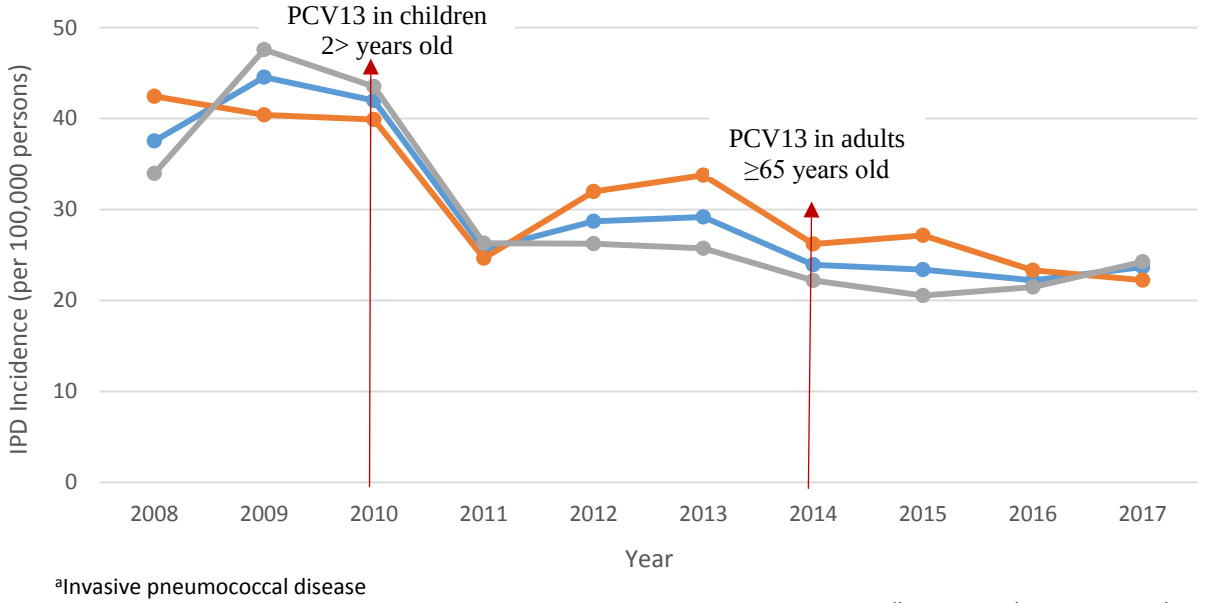


Figure 1B: IPD[a] incidence in adults ≥65 years old in Atlanta MSA[b] by race, 2008-2017



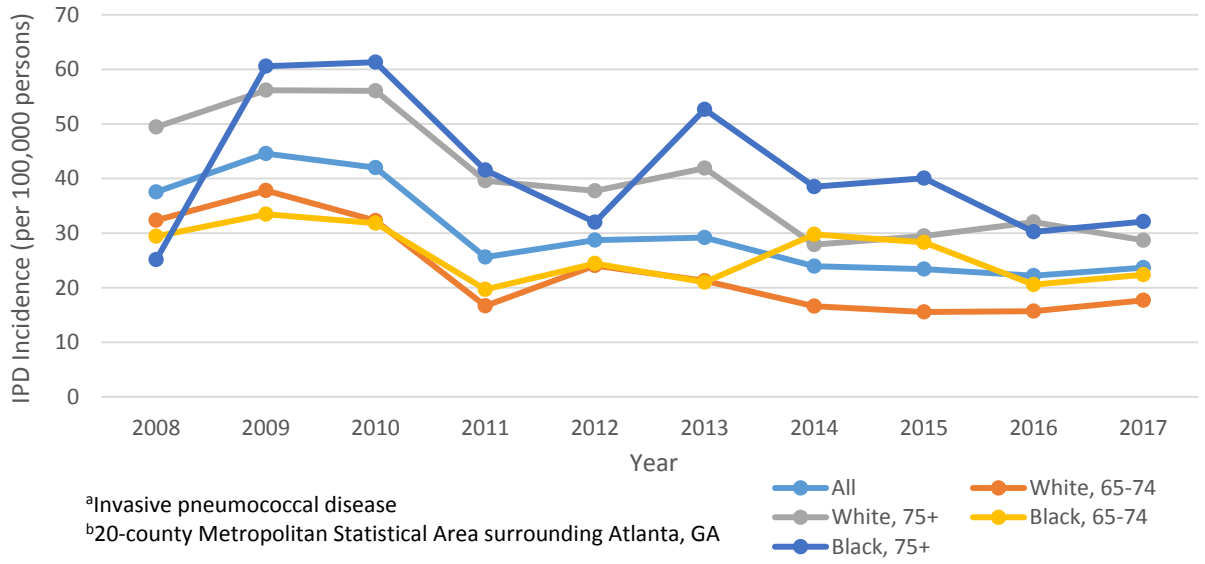
[a]Invasive pneumococcal disease
[b]20-county Metropolitan Statistical Area surrounding Atlanta, GA

Figure 1C: IPD[a] incidence in adults ≥65 years old in Atlanta MSA[b] by sex, 2008-2017



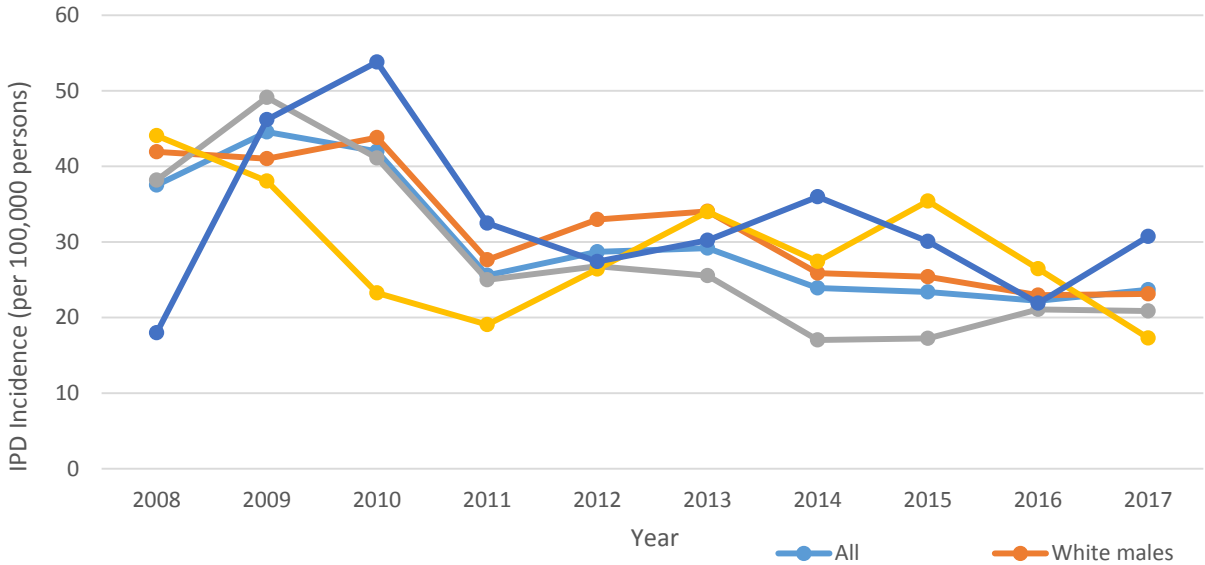
[a]Invasive pneumococcal disease
[b]20-county Metropolitan Statistical Area surrounding Atlanta, GA

Figure 1D: IPD[a] incidence in adults ≥65 years old in Atlanta MSA[b], race by age group, 2008-2017



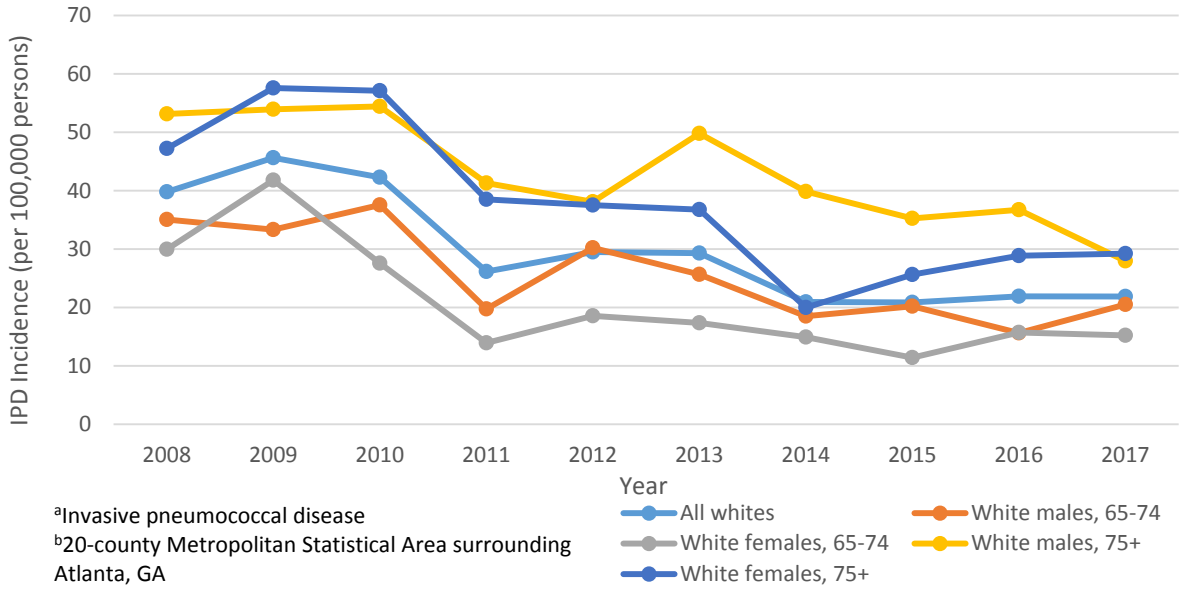
[a]Invasive pneumococcal disease
[b]20-county Metropolitan Statistical Area surrounding Atlanta, GA

Figure 1E: IPD[a] incidence in adults ≥65 years old in Atlanta MSA[b] by sex and race, 2008-2017



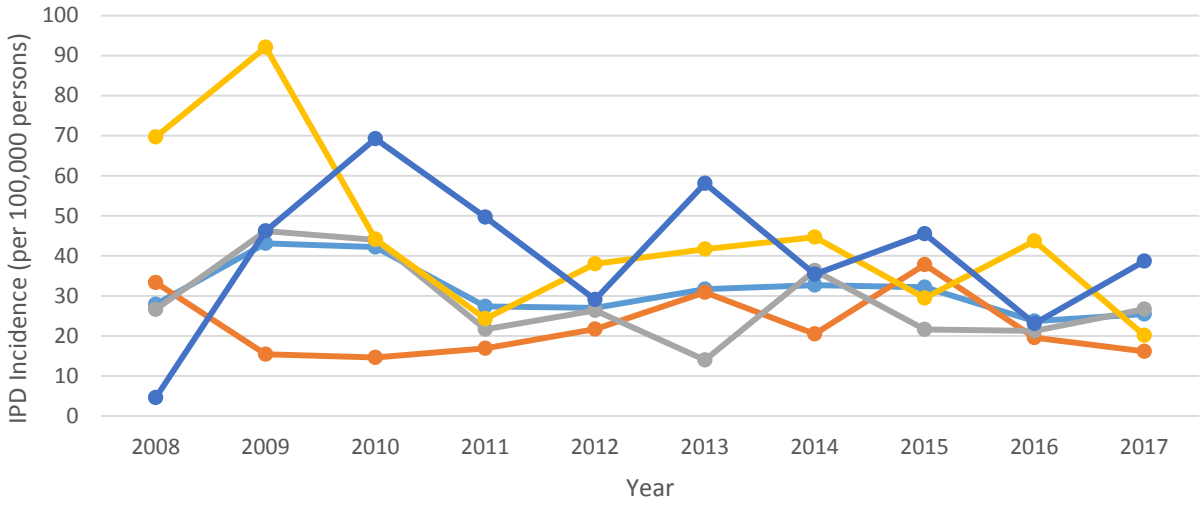
[a]Invasive pneumococcal disease
[b]20-county Metropolitan Statistical Area surrounding Atlanta, GA

Figure 1F: IPD[a] incidence in white adults ≥65 years old in Atlanta MSA[b] by sex and age group, 2008-2017



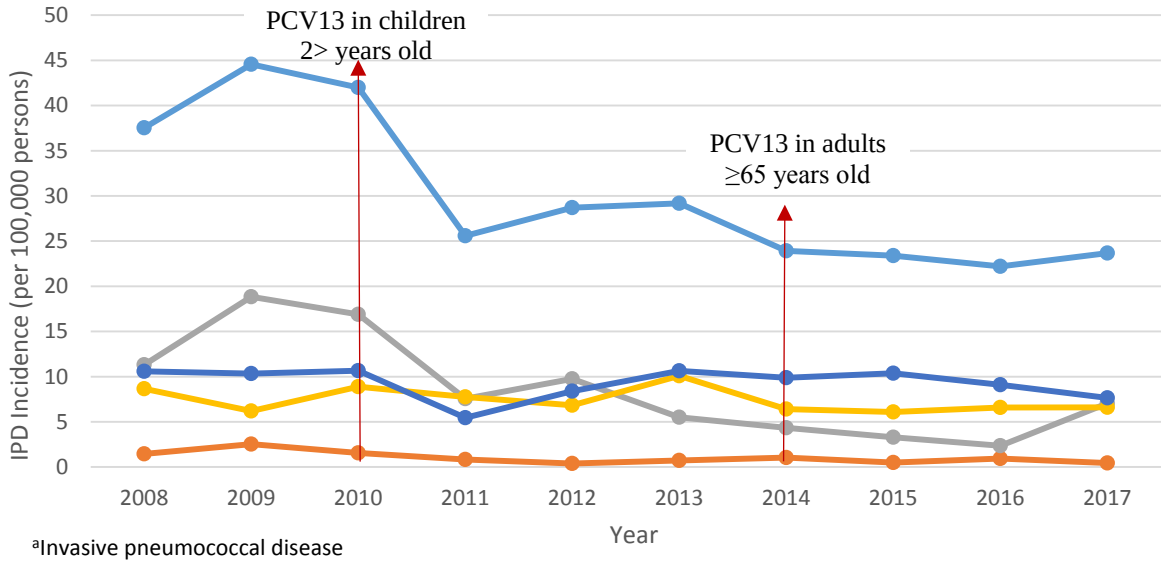
[a]Invasive pneumococcal disease
[b]20-county Metropolitan Statistical Area surrounding Atlanta, GA

Figure 1G: IPD[a] incidence in black adults ≥65 years old in Atlanta MSA[b] by sex and age group, 2008-2017



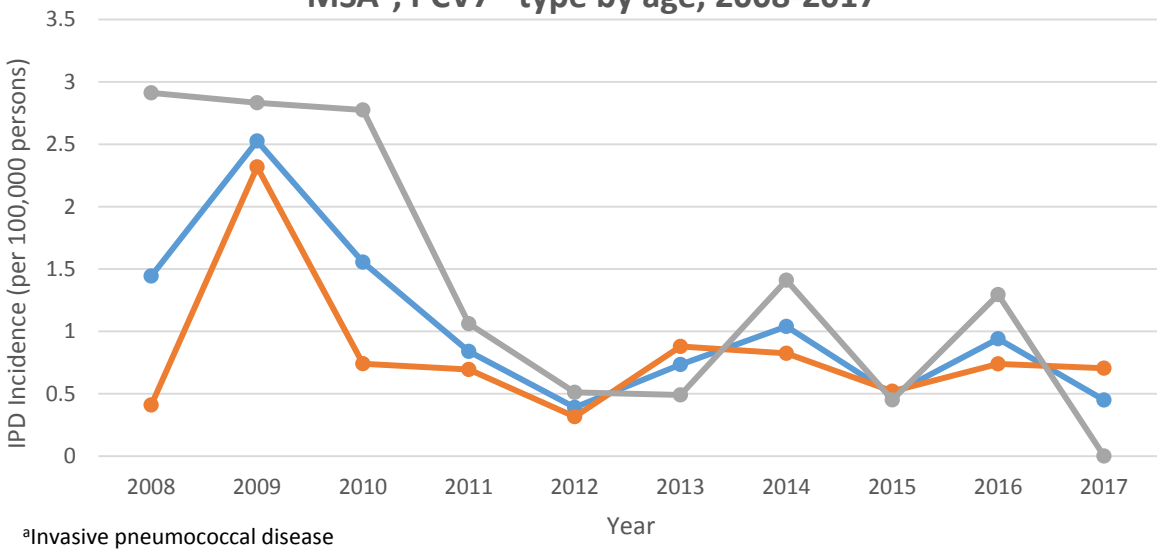
[a]Invasive pneumococcal disease
[b]20-county Metropolitan Statistical Area surrounding Atlanta, GA

Figure 2A: IPD[a] incidence in adults ≥65 years old in Atlanta MSA[b] by serotype group, 2008-2017



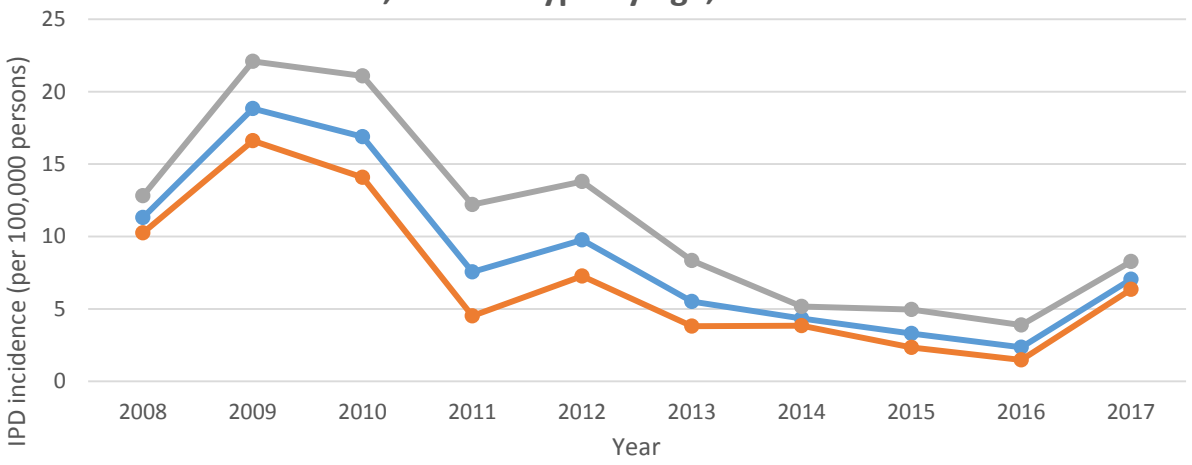
[a]Invasive pneumococcal disease
[b]20-county Metropolitan Statistical Area surrounding Atlanta, GA
*PCV7 type includes IPD serotypes 4, 6B, 9V, 14, 18C, 19F, 23F, and 6A
^PCV13 type includes IPD serotypes 19A, 7F, 5, 3, 1 and 6C
"PPV11 type includes IPD serotypes 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, and 33F

Figure 2B: IPD[a] incidence in adults ≥65 years old in Atlanta MSA[b], PCV7* type by age, 2008-2017



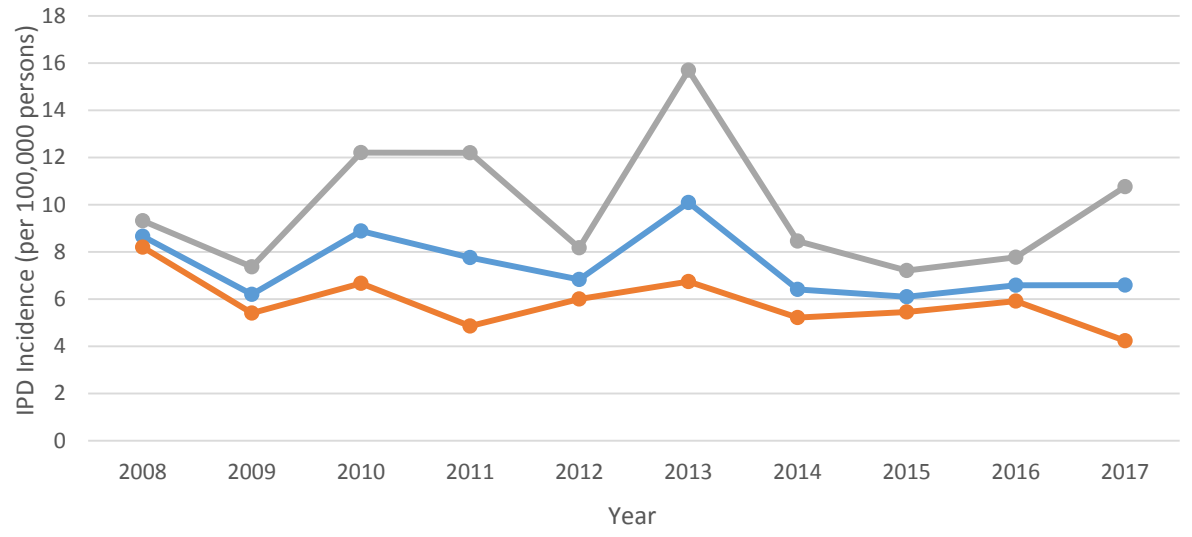
[a]Invasive pneumococcal disease
[b]20-county Metropolitan Statistical Area surrounding Atlanta, GA
*PCV7 type includes IPD serotypes 4, 6B, 9V, 14, 18C, 19F, 23F, and 6A

Figure 2C: IPD[a] incidence in adults ≥65 years old in Atlanta MSA[b], PCV13^ type by age, 2008-2017



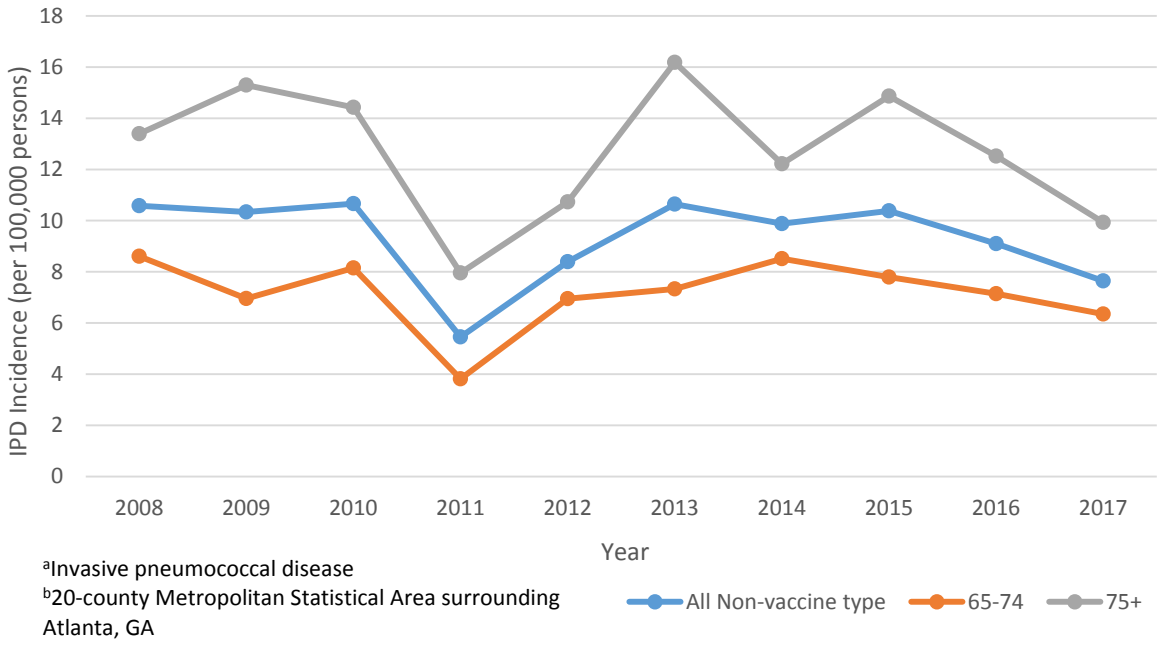
[a]Invasive pneumococcal disease
[b]20-county Metropolitan Statistical Area surrounding Atlanta, GA
^PCV13 type includes IPD serotypes 19A, 7F, 5, 3, 1, and 6C

Figure 2D: IPD[a] incidence in adults ≥65 years old in Atlanta MSA[b], PPV11" type by age, 2008-2017



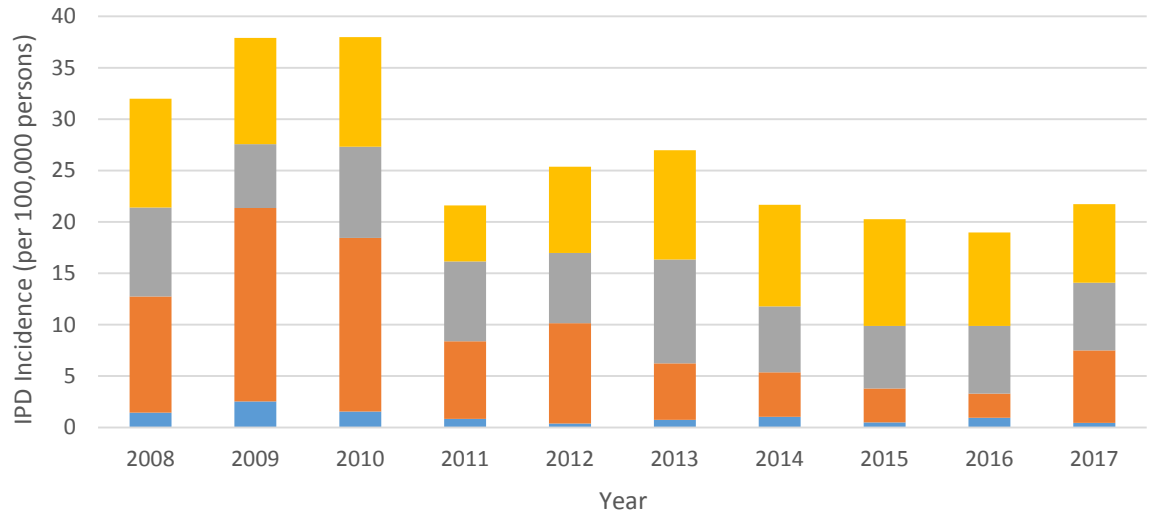
[a]Invasive pneumococcal disease
[b]20-county Metropolitan Statistical Area surrounding Atlanta, GA
"PPV11 type includes IPD serotypes 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, and 33F

Figure 2E: IPD[a] incidence in adults ≥65 years old in Atlanta MSA[b], Non-vaccine type by age, 2008-2017



[a]Invasive pneumococcal disease
[b]20-county Metropolitan Statistical Area surrounding Atlanta, GA

Figure 3A: IPD[a] incidence in adults ≥65 years old in Atlanta MSA[b] by serotype group, 2008-2017



[a]Invasive pneumococcal disease
[b]20-county Metropolitan Statistical Area surrounding Atlanta, GA
*PCV7 type includes IPD serotypes 4, 6B, 9V, 14, 18C, 19F, 23F, and 6A
^PCV13 type includes IPD serotypes 19A, 7F, 5, 3, 1, and 6C
"PPV11 type includes IPD serotypes 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, and 33F