Distribution Agreement

Signature:

_______________________________ _______________

Jennifer Oliver Spicer Date

Socioeconomic and racial disparities in invasive pneumococcal disease among children less than five years of age in the post-pneumococcal conjugate vaccine era

By

Jennifer Oliver Spicer

Master of Public Health

Epidemiology

John E. McGowan Jr., MD

Faculty Thesis Advisor

Monica M. Farley, MD

Thesis Field Advisor

Socioeconomic and racial disparities in invasive pneumococcal disease among children less than five years of age in the post-pneumococcal conjugate vaccine era

By

Jennifer Oliver Spicer

Bachelor of Science

University of Georgia

2007

Faculty Thesis Advisor: John E. McGowan Jr., MD

Field Advisor: Monica M. Farley, MD

An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
In partial fulfillment of the requirements for the degree of
Master of Public Health
In Epidemiology
2012

Socioeconomic and racial disparities in invasive pneumococcal disease among children less than five years of age in the post-pneumococcal conjugate vaccine era

By Jennifer Oliver Spicer

Objective: This study analyzed the independent effect of census tract-level socioeconomic characteristics on rates of IPD in children less than five years of age in addition to race-stratified estimates.

Methods: Socioeconomic and racial trends in IPD incidence in the post-heptavalent pneumococcal conjugate vaccine (PCV7) era were examined for 905 children less than five years of age. Data were obtained through active laboratory- and population-based surveillance from the Centers for Disease Control and Prevention-sponsored Georgia Emerging Infections Program for the 20-county Metropolitan Atlanta region in Georgia for the time period of 2001 through 2009. Incidence rates were calculated by race and socioeconomic characteristics using data from the 2000 US Census. Trends in IPD were determined by chi-squared tests for trend, and rate ratios (RRs) and 95% confidence intervals (CIs) were estimated using Poisson regression.

Results: For 2001 through 2009, the average annual incidence of invasive pneumococcal disease was 46.1 cases per 100,000 in black children and 28.9 cases per 100,000 in white children (RR=1.60; 95% CI 1.49, 1.71). Race-stratified incidence rates demonstrated statistically significant linear trends between IPD rates and some census tract-level socioeconomic factors. In white children, there were trends of increasing IPD incidence as the percentage of low-income houses increased ($p = 0.007$). In black children, trends of increasing IPD incidence were observed as median household increased ($p = 0.005$), as census tract poverty decreased ($p = 0.009$), and as crowding decreased ($p < 0.001$). After adjusting for sex and race, only three socioeconomic measures showed significant associations with IPD incidence in at least one of their strata: percentage household crowding (RR=0.75; 95% CI 0.59, 0.96), percentage low-income households (RR=1.38; 95% CI 1.03, 1.84), and census tract median household income (RR=1.34; 95% CI 1.07, 1.69). Race was still a significant predictor of disease even after controlling for sex and socioeconomic characteristics.

Discussion: The estimated effect of socioeconomic characteristics on IPD rates differs by race. Although crowding, percentage low-income households, and median household income account for some health disparities in IPD rates in children, race remains an independent risk factor for IPD in children in the post-PCV7 era.

Socioeconomic and racial disparities in invasive pneumococcal disease among children less than five years of age in the post-pneumococcal conjugate vaccine era

By

Jennifer Oliver Spicer

Bachelor of Science

University of Georgia

2007

Faculty Thesis Advisor: John E. McGowan Jr., MD

Field Advisor: Monica M. Farley, MD

A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
In partial fulfillment of the requirements for the degree of
Master of Public Health
In Epidemiology
2012

Acknowledgements

I would like to thank Monica Farley and Wendy Baughman for their help in providing me with a dataset and in developing my thesis plan. Their knowledge and guidance was instrumental in teaching me how to adequately interpret my results, and I appreciate their endless support throughout my entire learning process.

I would like to thank John McGowan for his guidance in the development of my thesis question and his feedback on my thesis manuscript.

I would like to thank Amy Holst, Sasha Schlicher, and Stepy Thomas for their help in preparing my initial dataset and troubleshooting all of my data issues with me.

I would like to thank Harland Austin, Penny Howard, and Michael Kramer for their suggestions in developing my analysis plan.

I would like to thank my parents, Tom and Susan Oliver, and my stepmom Kim Oliver for their support throughout my education, even when that meant that I wasn't able to spend as much time at home as we all would have wished.

Finally, I would like to thank my husband, Jason Spicer, for his unwavering support throughout my education. I have spent many long hours working on my thesis and my courses, and he always offered to help out in any way possible.

Table of Contents

BACKGROUND & LITERATURE REVIEW

Introduction

Streptococcus pneumoniae is a leading cause of pneumonia and meningitis both worldwide and within the United States (1, 2). Even though an adult vaccine has been available since 1977 and a childhood vaccine has been available since 2000, there is still significant morbidity and mortality associated with *S. pneumoniae* infections in the United States (3-5). In 2004, the United States had an estimated 4.0 million episodes of *S. pneumoniae* infection with approximately 774,000 emergency department visits, 445,00 hospitalizations, and 22,000 deaths (2). These illnesses resulted in an estimated $3.5 billion in direct costs to the healthcare system (2).

With the recent focus on health disparities in the public health field, the Department of Health and Human Services has requested baseline data on the racial and socioeconomic health disparities of invasive *S. pneumoniae* infection in the United States with a specific focus on groups targeted by pneumococcal vaccines—the young and elderly (6). Unfortunately, no baseline data concerning the socioeconomic health disparities of invasive *S. pneumoniae* infection in children was available for the Healthy People 2010 report (7). Collecting and analyzing information on the interaction of racial and socioeconomic disparities in invasive *S. pneumoniae* infection is important given the focus of Healthy People 2020 to identify and quantify social determinants of health (8). This study will provide baseline data for racial and socioeconomic disparities in invasive *S. pneumoniae* infection in children less than five years old in the post-PCV7 vaccine era.

Epidemiology of *S. pneumoniae*

S. pneumoniae causes bacterial disease in both children and adults. The spectrum of disease includes localized infections, such as otitis media and sinusitis, and more severe disease such as pneumonia, bacteremia, and meningitis. Invasive disease is defined as the isolation of *S.*

pneumoniae from a normally sterile body site such as blood or cerebrospinal fluid. Because of the significant morbidity and mortality related to it, invasive pneumococcal disease is often the focus of surveillance efforts in the United States.

The introduction of the childhood heptavalent pneumococcal conjugate vaccine (PCV7) in 2000 resulted in a significant reduction in invasive pneumococcal disease in children less than five years (5, 9-12). In 1999, prior to the introduction of PCV7, the incidence of invasive pneumococcal disease was 87.4 cases per 100,000 children younger than five years (13). In 2010, ten years after the introduction of the vaccine, the incidence of invasive pneumococcal disease was 18 cases per 100,000 children younger than five years (14). The distribution of the manifestations of invasive pneumococcal disease has also changed since the introduction of PCV7 resulting in an increase in the percentage of bacteremic pneumonia cases (53.7% to 69.3%), a decrease in the percentage of bacteremia without focus cases (37.6% to 17.9%), and a similar percentage of meningitis cases (5.2% to 6.0%) (13, 14). Vaccine uptake has been shown to vary by race, poverty, and education, which suggests that reductions in the incidence of pneumococcal disease likely differs according to racial and socioeconomic groups (11, 15, 16).

Besides race and socioeconomic status, risk factors for *S. pneumoniae* infection include gender, age, preceding viral respiratory infections, chronic medical conditions, group child care, exposure to smoking, lack of breastfeeding, and non-private health insurance (10, 17, 18). Multiple studies have shown that rates of invasive pneumococcal disease are higher in male children, although this observed difference does not consistently demonstrate statistical significance (10, 18). Invasive pneumococcal disease is more prevalent at the extremes of age, especially in children younger than five years and adults older than 65 years (4, 10, 19). Chronic medical conditions in children that increase the risk for invasive pneumococcal disease include chronic cardiopulmonary disease, diabetes mellitus, asplenia, liver disease, neurological malformations, chronic renal failure, cancer, transplants, immunosuppressive medications, sickle cell disease, and HIV (17, 20). HIV, sickle cell disease, and hematological malignancies, in particular, predispose children to invasive pneumococcal disease, with the risk of disease in those populations shown to be approximately fifty times greater than in healthy children (17, 21, 22).

Racial Disparities in Invasive Pneumococcal Disease

Rates of invasive pneumococcal disease are typically higher in non-white populations as compared to whites. Certain small subpopulations have been found to have markedly increased rates of invasive pneumococcal disease as compared to the general population. American Indians and Alaskan Natives have between two and eight times higher incidence rates of invasive pneumococcal disease as compared to the general population, and these higher rates of disease are observed in all age groups, particularly in children less than two years of age (4, 23). In the 1980s, the White Mountain Apache tribe in eastern Arizona had the highest rates of disease of any known United States population with 2,396 cases per 100,000 persons for children aged between one and two years (24). Interestingly, multiple studies have demonstrated that the rates of invasive pneumococcal disease in Hispanic populations are similar to those of white populations (18, 19).

In the United States, black populations have higher rates of disease than white populations. Prior to the introduction of PCV7, most studies demonstrated that blacks had two to three times higher rates of invasive pneumococcal disease compared to whites in all age groups even after controlling for factors such as income, underlying disease, and sex (25-27). Racial disparities decreased with increasing age, and some studies demonstrated that race was not an independent risk factor for invasive pneumococcal disease among elderly individuals (4, 26). Since the introduction of the PCV7, racial disparities between black and white populations have decreased, but racial differences in invasive pneumococcal disease still exist even after adjusting for potential confounders (10, 20, 28-31). Many possible explanations exist for these racial disparities including differences in socioeconomic status, underlying disease rates, and genetic predisposition to particular *S. pneumoniae* seroptypes.

Socioeconomic Health Disparities

Although racial disparities in health have been well characterized in the literature, socioeconomic factors, such as income, poverty, wealth, education, and crowding, have been increasingly recognized as causes of health disparities. Recent studies have shown that socioeconomic factors can affect health in varying ways. Infectious diseases such as chlamydia, gonorrhea, syphilis, tuberculosis, and influenza are typically associated with high levels of poverty and crowding (32-34). Intentional weapons-related injuries, low birth weight, and childhood lead poisoning are also more prevalent in areas with high poverty and low education levels (33, 35).

Although adverse health outcomes are typically associated with "worse" socioeconomic measures (e.g. high crowding, low education levels, high poverty, etc.), some studies have found the inverse to be true. One study found that the age-adjusted rates of breast cancer were higher in areas with a high median household income and low neighborhood poverty levels. In the same study, lung cancer and cervical cancer were associated with low median household income and high neighborhood poverty levels whereas colon cancer was not significantly associated with either median household income or neighborhood poverty levels (36). All of these examples illustrate that socioeconomic status and health are often interrelated, but the direction of the relationship depends on the disease being examined.

Geocoding and Area-Based Socioeconomic Measures

Analyzing socioeconomic health disparities is a recent development in the public health field because few public health surveillance systems collect socioeconomic data. To overcome this issue, the Harvard Public Health Disparities Geocoding Project has developed a standardized method for including socioeconomic variables in public health research (37). Instead of relying on limited or absent socioeconomic data in surveillance systems, they recommend using population-level socioeconomic characteristics collected through census forms. By using the addresses of individuals in public health datasets, it is possible to assign each person to a small geographic area on a map in a process called geocoding; then, using the socioeconomic data collected on census forms, it is possible to obtain information on the average educational level, median household income, percentage of household crowding, and other environmental socioeconomic characteristics of the area in which that individuals lives. Although this method does not necessarily identify the individual's socioeconomic status, it provides information about the social environment of the individual. These environmental socioeconomic measures are referred to as area-based socioeconomic measures (ABSMs).

Census data is collected from and compiled for many different geographic areas—state, city, county, zip code, census tract, and block group. In the past, studies used zip codes to connect census data to individuals, but zip codes are large, heterogeneous areas containing individuals from a variety of socioeconomic backgrounds (38). In contrast, the U.S. census bureau defines census tracts as permanent geographic areas containing between 2,500 and 8,000 residents with similar social and economic characteristics. The Harvard Public Health Disparities Geocoding Project examined the relationship between socioeconomic variables and the population health outcomes of three different geographic levels—zip codes, census tracts, and block groups—and found that census tract level analysis yields the most consistent results while still successfully matching most individuals to a geographic region (39).

Through their project, the Harvard investigators also developed and tested a number of standardized ABSMs collected at the census tract level that they recommend using to assess socioeconomic health disparities. The ABSMs suggested by the Harvard Public Health Disparities Geocoding Project are not necessarily proxies for individual-level socioeconomic characteristics but rather provide complimentary information about an individual's socioeconomic environment (37, 40). Since census tracts are relatively small, homogenous areas, all individuals within those areas are more likely to experience the same socioeconomic environment. Studies have shown that the use of ABSMs or individual-level socioeconomic characteristics in health research results in similar conclusions about associations and their direction (positive or negative); ABSMs, however, tend to underestimate the effect of socioeconomic status on health outcomes as compared to the individual-level variables (20, 37).

Socioeconomic Measures and *S. pneumoniae* Infection

Many studies include socioeconomic variables in an attempt to "control" for socioeconomic confounders rather than looking at socioeconomic variables as exposures. With the recent focus on health disparities, studies like the Harvard Public Health Disparities Geocoding Project are using socioeconomic factors to describe health disparities and identify possible mechanistic pathways through which socioeconomic factors affect health. For this analysis, a number of socioeconomic factors were identified that could potentially be mechanistically related to invasive pneumococcal disease: income, poverty, wealth, education, and crowding.

Income, poverty, and wealth all measure the financial status of a neighborhood, which could affect invasive pneumococcal disease rates in a variety of manners. Impoverished neighborhoods could have higher rates of invasive pneumococcal disease if individuals fail to get vaccinated or avoid early medical attention due to the prohibitive costs of medical care; conversely, impoverished neighborhoods could have lower rates of disease if free clinics in the area result in increased vaccine rates. Previous studies examining household income as a risk factor for invasive pneumococcal disease have found that low household income is associated with a higher rate of disease (18, 20, 26, 27, 29, 41). In one of the studies, both self-reported and census tract level household income data was used; although a significant association was found when using self-reported income, no significant difference in invasive pneumococcal disease rates was found when using census tract level income data (20). In contrast, two studies, one in the pre-PCV7 era and one in the post-PCV7 era, found that rates of invasive pneumococcal disease were highest in either the middle- or high-income strata (29, 42). When trends were examined stratified on age or race, the conclusions regarding the association between invasive pneumococcal disease rates and income differed depending on the study (26, 27, 29, 41).

Education is another socioeconomic variable that could potentially affect the incidence of invasive pneumococcal disease in a community. Education affects knowledge and attitudes about vaccination and other disease prevention strategies. Individuals with higher education could have a tendency to ask for vaccines because they are aware of the benefits of vaccination; alternatively, individuals with higher education could be more likely to refuse vaccination because they are aware of the potential side effects of vaccination. Two studies looking at self-reported individual-level education found that lower levels of education were associated with higher rates of invasive pneumococcal disease (18, 20).

Crowding is the final socioeconomic factor that will be examined. Respiratory diseases, such as *S. pneumoniae*, are typically associated with crowding, since the causative organisms are spread through respiratory droplets or secretions. Previous outbreaks of *S. pneumoniae* have been associated with closed communities with high levels of crowding (43-45). In a case-control study examining risk factors for invasive pneumococcal disease, sharing a bedroom with more than one other person was associated with an increased risk of invasive pneumococcal disease (18).

All of these studies suggest that socioeconomic factors are associated with invasive pneumococcal disease rates. The direction of the association, however, depends on the population studied, suggesting that age, race, and other factors affect the relationship.

Thesis Rationale and Objective

Describing the socioeconomic health disparities of invasive pneumococcal disease in vaccine-targeted populations—children < 5 years and adults > 65 years—is listed as an objective for *Healthy People 2020* (6). Although eight previous studies have examined the association between socioeconomic status and invasive pneumococcal disease, only three of those studies have specifically described this relationship in children younger than five years (Table 1) (18, 26, 27). Two of those three studies occurred before the introduction of the PCV7 vaccine, which has been shown to alter the association between socioeconomic factors and invasive pneumococcal disease rates, especially within particular racial groups (29). The one post-vaccination study that specifically looked at the effect of socioeconomic status in children failed to analyze race-stratified estimates of invasive pneumococcal disease rates even though socioeconomic status has been shown to affect racial groups differently (18, 29).

This analysis will investigate the association between census tract socioeconomic factors and rates of invasive pneumococcal disease in children under five years of age in the post-PCV7 vaccination era using surveillance data from the Georgia Emerging Infections Program (EIP) office. Socioeconomic variables will be chosen based on the recommendations of the Harvard Health Disparities Geocoding Project in addition to considering which of those variables could have a mechanistically plausible association with invasive pneumococcal disease rates. Results will be stratified by race since previous studies suggest that an interaction exists between socioeconomic status and race (29, 46). I hypothesize that the rate of invasive pneumococcal disease in children less than five years of age will be higher in areas with lower socioeconomic status (i.e. high poverty, low household income, low wealth, low educational level, or high crowding). In addition, I hypothesize that the gradient of socioeconomic disparities in invasive pneumococcal disease rates will be greater in white children as compared to black children.

METHODS

Study Population

The U.S. Centers for Disease Control and Prevention's Active Bacterial Core surveillance/Emerging Infections Program (EIP) network consists of ten state health departments and their collaborators who conduct active population-based laboratory surveillance for a variety of infectious diseases, including invasive *Streptococcus pneumoniae* infection. Cases are identified through weekly calls to clinical laboratories and periodic audits of laboratory records. Clinical and demographic data are collected from medical records for each case, recorded on a case report form, and entered into the EIP database. In Georgia, this surveillance area consists of the 20-country Metropolitan Atlanta area.

For this analysis, the study population included all cases of invasive pneumococcal disease in children less than five years of age identified through active population-based laboratory surveillance in the 20-county Metropolitan Atlanta area from 2001 – 2009. Invasive pneumococcal disease was defined as any case where *S. pneumoniae* was isolated from a normally sterile body site including blood, cerebrospinal fluid, pleural fluid, peritoneal fluid, pericardial fluid, joint, muscle, bone, or other internal body site. The time period 2001 – 2009 was chosen to represent the post-PCV7 era since the vaccine was introduced in mid-2000 (9).

Geocoding and US Census Data

According to the U.S. Census Bureau, census tract are small geographic areas containing between 2,500 and 8,000 individuals with similar socioeconomic conditions (38). Census tracts are the most appropriate geographic regions to use when examining the effect of socioeconomic variables on health outcomes (35, 37). The 20-county Atlanta Metropolitan surveillance area contained 660 census tracts according to the 2000 U.S. Census. Using addresses obtained from the Georgia EIP case report forms, each case in this analysis was assigned to a census tract from the 2000 U.S. Census using ArcView/ArcGIS 10.1 (ESRI, Redlands, CA). After assigning cases to census tracts, race- and gender-specific population denominators for children less than five years were obtained from the 2000 U.S. Census for each census tract.

Socioeconomic Variables

Since most public health databases do not contain socioeconomic data, area-based socioeconomic measures from U.S. Census data have been recommended for analyzing socioeconomic health disparities (37). These area-based socioeconomic measures represent the environmental socioeconomic characteristics of individuals and add complimentary information to any individual-level socioeconomic information collected in studies. The socioeconomic variables used in this analysis were based on those recommended by the Harvard Public Health Disparities Geocoding Project (36).

Socioeconomic measures for each census tract were downloaded from the U.S. Census 2000 Summary 3 File which contains population and household data from the census's log form questionnaire. Since this information is only collected in the decennial census, data from the 2000 census was used for all cases in this analysis. Variables were created to represent census tract level measures of poverty, wealth, income, education, and crowding. Those variables were categorized using percentile distributions, such as quintiles, or *a priori* delineations suggested by the Public Health Disparities Geocoding Project.

Census tract poverty was defined as the percentage of the households in the census tract with incomes below the federally defined poverty level and was categorized using quintiles and *a priori* categories. The *a priori* categorization was stratified into four levels: 0 to 4.9%, 5.0 to 9.9%, 10.0 to 19.9%, and greater than 20% of households living below the federally defined poverty level. Using quintiles, census tract poverty was stratified into five levels: 0 to 3.3%, 3.4% to 5.8%, 5.9% to 9.0%, 9.1% to 15.1%, and greater than 15.2% of households living below the federally defined poverty level.

Census tract wealth was defined as the percentage of owner-occupied homes worth greater than or equal to 400% of the U.S. median value of owned homes. This variable was categorized into four levels using *a priori* categorization: 0 to 4.9%, 5.0 to 9.9%, 10.0 to 19.9%, and greater than 20% of owner-occupied homes in the census tract worth greater than or equal to 400% of the U.S. median value of owned homes.

Income was defined as median household income. This data was used to create three income variables: median household income, low income, and high income. Median household income for each census tract was categorized into quintiles resulted in five levels: $0 to $35,416, $35,416 to $44,329, $44,330 to $52,935, $52,935 to $67,946, and greater than $67,946 median household income. Low income was defined as the percentage of households with a median household income less than 50% of the U.S. median household income. Low income was categorized into four levels: 0 to 4.9%, 5.0 to 9.9%, 10.0 to 19.9%, and greater than 20% of the households in the census tract with a median household income less than 50% of the U.S. median household income. High income was defined as the percentage of households with median household incomes greater than 400% of the U.S. median household income. High income was categorized into four levels: 0 to 4.9%, 5.0 to 9.9%, 10.0% to 19.9%, and greater than 20% of households in the census tract with median household incomes greater than 400% of the U.S. median household income.

Two variables were created to represent education: high education and low education. High education was defined as the percentage of persons in each census tract aged 25 years or older with at least a Bachelor's degree and was categorized into four levels: 0% to 14.9%, 15.0 to 24.9%, 25.0% to 39.9%, and greater than 40% of persons in the census tract aged 25 years or older with a Bachelor's degree or higher degree. Low education was defined as the percentage of persons in each census tract aged 25 years or older with less than a 12^{th} grade education, including those who completed 12^{th} grade but did not receive a degree. Low education was categorized into four levels: 0% to 14.9%, 15.0 to 24.9%, 25.0% to 39.9%, and greater than 40% of persons in the census tract aged 25 years and older without a high school degree.

Crowding was defined as the percentage of households in each census tract with equal to or greater than one person per room. This variable was categorized using quintiles and *a priori* categories. The *a priori* categorization was divided into four levels: 0% to 4.9%, 5.0% to 9.9%, 10.0% to 19.9%, and greater than 20% of households in the census tract with equal to or greater than one person per room. The quintile categorization was divided into five levels: 0% to 1.4%, 1.5% to 2.9%, 3.0% to 5.1%, 5.2% to 9.5%, and greater than 9.6% of households in the census tract with equal to or greater than one person per room.

Case Variables

In addition to socioeconomic factors, a number of case variables were included in this analysis because of their association with invasive pneumococcal disease. Race was the primary covariate of interest because of its known association with both socioeconomic status and invasive pneumococcal disease rates (28-30, 46). Race was classified as white, black, or other. Other race included Asian, American Indian/Alaskan Native, and Native Hawaiian/Other Pacific Islander races. For those cases missing race (12.3%), race was assigned according to the race that represented the majority of children less than five years of age within the case's census tract since analyses excluding those individuals with missing race yielded similar results.

Additional covariates of interest included sex, vaccination status, and the presence of underlying diseases known to predispose individuals to invasive pneumococcal disease. Sex was classified as male or female and was obtained from the case report form. Vaccination status was defined as yes if the individual had received at least one dose of the pneumococcal conjugate vaccine (PCV7 or PCV13) prior to the positive culture date, no if the individuals had received no doses of the vaccine prior to the positive culture date, and unknown if the individual's vaccination history could not be obtained after checking with the individual's physician office and the

Georgia Immunization Registry. The presence of underlying disease was coded as yes if the individual was identified to have an underlying disease that could predispose him to invasive pneumococcal disease, no if the individual had no underlying disease, and unknown if the patient's chart was unavailable for review. Underlying diseases that could predispose the individual to invasive pneumococcal disease included asthma, immunosuppressive therapy, sickle cell disease, solid organ malignancy, leukemia, premature birth, organ transplant, nephrotic syndrome, globulin deficiency, HIV/AIDS, or other disease.

Additional variables examined to describe the cases included age, clinical manifestation of disease, *S. pneumoniae* strain, hospitalization, length of hospital stay, and admission to the intensive care unit (ICU). Age was analyzed both as a categorical variable of age in years and a continuous variable of age in months. Clinical manifestation of disease refers to the type of infection cause by the organism and was coded as bacteremia without focus, meningitis, otitis media, pneumonia, or other (cellulitis, epiglottitis, hemolytic uremic syndrome, abscess, peritonitis, pericarditis, septic arthritis, osteomyelitis, empyema, endocarditis, soft tissue skin infection, streptococcal toxic shock syndrome, necrotizing fasciitis, or septic shock). *S. pneumoniae* strain was categorized as strains included in the PCV7 vaccine (4, 6B, 9V, 14, 18C, 19F, or 23F) or non-PCV7 strains (all other strains). Hospitalization was categorized as yes if the individual was hospitalized, no if the patient was not hospitalized, or unknown if this information was not obtainable. Length of hospital stay was a continuous variable recorded in days. Admission to the ICU was categorized as yes if the patient was admitted to the ICU during hospitalization, no if the patient was not admitted to the ICU during hospitalization, or unknown if this information was not available upon medical record review.

Statistical Analyses

Case information including sex, age, vaccination status, clinical manifestation of disease, underlying diseases, hospitalization status, admission to the ICU, length of hospital stay, and *S.*

pneumoniae strain was stratified on race. Statistical differences between white and black cases were examined using chi-square tests for categorical variables and t-tests for continuous variables.

Average annual incidence rates were calculated by dividing the average number of cases in 2001 to 2009 by the population of children under five years of age in the surveillance area according to the 2000 U.S. Census data. Stratified incidence rates were calculated for race, sex, and socioeconomic variable categories. The chi-squared test for trend was used to analyze trends in incidence for each socioeconomic variable. Incidence rates could not be stratified by age because the 2000 U.S. Census did not contain population denominators stratified on both age and race for children under five years of age.

Poisson regression was used to calculate rate ratios (RRs) and 95% confidence intervals (CIs). The dependent variable for Poisson regression was the number of invasive pneumococcal disease cases for each racial, gender, and socioeconomic category. Independent variables included race, gender, and a census-tract level socioeconomic measure. Only one socioeconomic variable was included per model. Interactions between race and socioeconomic variables were analyzed for each model, and race-specific rates were also reported. In order to identify if any of the socioeconomic measures explained racial disparities in invasive pneumococcal disease in children, ten independent models were created containing race, sex, one socioeconomic measure, and an interaction term for race and the socioeconomic measure if significant. Other race was excluded from models due to low numbers of cases. Adjusted RRs for all variables were reported.

Vaccination status and underlying disease could not be included in the model because denominator data did not exist for those variables at the census tract level. To assess the effect of those variables, cases were stratified on vaccination status or underlying disease, and race-stratified RRs were reported.

All statistical analyses were performed in SAS Version 9.3 (SAS Institute Inc, Cary, NC). Significance was defined as a 2-tailed p-value < 0.05.

RESULTS

From 2001 to 2009, there were 935 cases of invasive pneumococcal disease in children less than five years of age. A total of 905 (96.8%) cases were able to be geocoded. The remaining cases (n=35) were unable to be geocoded due to invalid address (69%) or post office box (31%). The cases consisted of approximately equal numbers of white (n=452) and black (n=415) children with a small number of children of other race (n=38) (Table 2). The majority of the cases were male (60.1%), and the mean age of the cases was 20.2 months (standard deviation (SD) = 14.6 months). Vaccination status was known for 57.9% of cases; for those with known status, 431/524 (82%) were known to have received at least one dose of the PCV7 vaccine, and most of the cases were infected with non-PCV7 *S. pneumoniae* strains (84.1%). Clinical manifestations of *S. pneumoniae* infection included bacteremia with unknown secondary focus (46.6%), pneumonia (30.8%), otitis (13.4%), meningitis (7.6%) and other conditions (6.6%). Hospitalization occurred in 43.9% of cases with a median hospital stay of 5.0 days (interquartile range (IQR) = 7.0 days). Very few cases were admitted to the intensive care unit (0.8%), although ICU admission status was unknown in the majority of cases (66.4%). White and black children with invasive pneumococcal disease differed significantly by average age (white=18.9 months, black=21.2 months, p=0.024) and by clinical manifestation of disease. The prevalence of pneumonia among black cases was higher than among white cases (35.2% vs. 26.6%; p-value = 0.006), whereas the prevalence of meningitis among white cases was higher than among black cases (10.0% vs. 5.5%; p-value = 0.016).

Most of the cases were known to have no underlying diseases predisposing them to invasive pneumococcal disease (69.6%). Among those with underlying diseases, asthma was the most prevalent (n=82), followed by immunosuppressive therapy (n=23), sickle cell disease (n=21), and solid organ malignancies (n=17) (Table 3). Diseases significantly more prevalent in blacks cases as compared to white cases included asthma (n=49 vs. n=29) and sickle cell disease (n=21 vs. n=0). Other illnesses were significantly more prevalent in white cases compared to black cases; these were solid organ malignancies (n=14 vs. n=3), leukemia (n=10 vs. n=1), and immunosuppressive therapy (n=21 vs. n=2).

According to the U.S. Census 2000 data, the Metropolitan Atlanta surveillance area contained 307,010 children less than five years of age of which 56.7% were white, 32.6% were black, and 10.7% were of another race including American Indian/Alaskan Native, Asian, or Hawaiian/Pacific Islander (Table 4). Black children were more likely to live in census tracts with high percentages of poverty and low percentages of wealth than white children (Figures 1 - 3). A larger proportion of white children lived in census tracts with high median household incomes compared to black children (Figures 4 – 6). A higher percentage of white children lived in census tracts where individuals graduated from high school and obtained a Bachelor's degree as compared to black children (Figures 7 and 8). A larger population of black children lived in census tracts with high levels of crowding compared to white children (Figures 9 and 10).

Among the total population, chi-squared trend analysis revealed a statistically significant linear trend between invasive pneumococcal disease rates in children and all of the area-based socioeconomic measures except for crowding (Table 5). Invasive pneumococcal disease incidence rates increased with increasing levels of poverty and lack of a high school degree, and decreased with increasing levels of wealth and increasing median household income increased.

The rate of invasive pneumococcal disease differed significantly by sex and race (Table 6). Females had lower rates of disease than males (RR=0.70, 95% CI=0.65, 0.74). The rate of invasive pneumococcal disease in black children was 1.60 times the rate in white children (95% confidence interval (CI) = 1.49, 1.71).

After stratifying invasive pneumococcal disease incidence rates by race, statistically significant linear trends between disease incidence and area-based socioeconomic measures were observed only for low-income census tracts among white children ($p=0.007$), and for poverty ($p=0.009$), median household income ($p=0.005$), and crowding ($p<0.001$) among black children (Table 7). Among black children, the incidence of invasive pneumococcal disease decreased with increasing levels of poverty (Figures 11 and 12), increased with increasing median household income (Figure 13), and decreased with increasing household crowding (Figures 14 and 15). Among white children, the incidence of invasive pneumococcal disease increased as the percentage of households in the census tract with low income increased; among black children, the opposite trend was seen, but it was not a statistically significant linear trend (Figure 16). No significant trends were observed in white or black children for census tract wealth, high income, low education, or high education (Figures 17-20).

For almost all socioeconomic measures, black children had significantly higher rates of invasive pneumococcal disease than white children when comparing individuals within the same socioeconomic level (Table 8). For poverty, significant differences between black and white children within the same poverty level were seen when using the *a priori* categorization of the variable, but significant differences in rate where not seen when using the quintile categorization of the variable. All of the other socioeconomic measures showed significant differences in invasive pneumococcal disease rates between black and white children within at least one, if not all, of the categories of each variable.

Restricting the analysis to children without underlying diseases did not change the results of the analysis (Table 9). Census tracts with the highest percentage of household poverty had higher rates of disease than census tracts with the lowest percentage of household poverty in the total population both among those with underlying disease (RR=1.41, 95% CI=1.03, 1.92) and without underlying disease (RR=1.22, 95% CI 1.01, 1.47). High poverty levels led to higher rates of disease in white populations with underlying disease (RR=5.48, 95% CI 1.97, 15.21) and without underlying disease (RR=1.43, 95% CI 1.01, 2.01); however, among black children, high poverty was significantly associated with lower rates of disease, but only among children without underlying disease (RR=0.64, 95% CI 0.43, 0.95). High percentages of census tract crowding was associated with lower rates of disease among black children both with underlying disease

(RR=0.42, 95% CI 0.18, 0.96) and without underlying disease (RR=0.65, 95% CI 0.48, 0.88), but there was no statistically significant association among white children.

Stratifying the results on vaccination status resulted in significant differences in the association between socioeconomic measures and invasive pneumococcal disease rates (Table 10). Among the total population, high census tract poverty levels was associated with increased rates of disease in unvaccinated individuals (RR=4.47, 95% CI 2.97, 6.74) but showed no association in vaccinated individuals (RR=0.87, 95% CI 0.66, 1.15). Among black children, high poverty levels resulted in lower rates of disease among vaccinated individuals (RR=0.47, 95% CI 0.29, 0.75) but higher rates of disease among unvaccinated individuals (RR=4.70, 95% CI 1.61, 13.76). Among the total population, high levels of census tract crowding were associated with lower rates of disease in vaccinated individuals (RR=0.72, 95% CI 0.57, 0.92), but higher rates of disease in unvaccinated individuals (RR=1.93, 95% CI 1.19, 3.13). Among black children, high levels of census tract crowding also was associated with lower rates of disease in vaccinated individuals (RR=0.51, 95% CI 0.35, 0.75) but not in unvaccinated individuals (RR=2.13, 95% CI 0.71, 6.42).

How each area-based socioeconomic measure affected racial disparities in invasive pneumococcal disease was investigated by analyzing ten separate models that adjusted for sex, race, one area-based socioeconomic measure, and an interaction term between race and the socioeconomic measure if appropriate. After adjusting for sex and race, only percentage of census tract household crowding (RR=0.75; 95% CI 0.59, 0.96), percentage of census tract low-income households (RR=1.38; 95% CI 1.03, 1.84), and census tract median household income (RR=1.34; 95% CI 1.07, 1.69) showed significant associations with invasive pneumococcal disease in children in at least one of their strata (Tables 11-14). In each model, black race was still significantly associated with increased rates of invasive pneumococcal disease. Socioeconomic factors did not appear to explain racial disparities observed in childhood invasive pneumococcal disease.

DISCUSSION

This was the first study to examine the race-stratified effect of area-based socioeconomic measures on invasive pneumococcal disease rates in children in the post-PCV7 era. The results of this analysis demonstrated that although some area-based socioeconomic measures are associated with invasive pneumococcal disease rates, none of those associations account for the racial disparities seen in invasive pneumococcal disease rates. After controlling for area-based socioeconomic measures, disease rates in black children were still 1.56 to 2.39 times the rate of disease in white children indicating that socioeconomic status does not fully explain racial disparities in invasive pneumococcal disease in children.

This analysis showed that as socioeconomic status worsened (e.g. lower educational level, higher household poverty, etc.), rates of invasive pneumococcal disease typically increased although not all trends were statistically significant. After controlling for race and sex in the multivariate analyses, only median household income and crowding were significantly associated with invasive pneumococcal disease rates in children less than five years of age. Those results highlight that socioeconomic measures are not exchangeable when examining health outcomes indicating that socioeconomic variables should be chosen carefully based on their mechanistic plausibility for causing disease.

Like some previous studies, no significant association was found between most of the area-based socioeconomic factors and invasive pneumococcal disease rates. For example, one study from the pre-PCV7 era found that in children less than five years of age, there was no significant trend in invasive pneumococcal disease rates across income brackets (27). Although a trend is typically observed in adults, this trend might be absent in children because government insurance programs allow almost all children to receive health insurance and medical attention, narrowing the gap between medical care access for the rich and poor. Alternatively, that trend may be because high-income families are more likely to use group day care than low-income families, which could raise the disease risk of high-income children to that of low-income children (47).

It is also possible that there is an association between socioeconomic factors and invasive pneumococcal disease rates in children but that this study did not find those associations. Previous studies have shown that area-based socioeconomic measures tend to underestimate the effect of socioeconomic factors on outcomes (37). In one particular study, no significant association was observed between census block group income levels and invasive pneumococcal disease rates even though a significant association was observed when using self-reported income (20). In addition, it is possible that the socioeconomic measures are not fully representing the relevant exposures. For example, the number of years of schooling may not matter as much as the quality of schooling does. Unfortunately, socioeconomic variables used in this study only measured quantitative data, such as years of schooling or income, rather than more indirect qualitative data such as quality of education or ability to use income effectively.

The association between socioeconomic factors and invasive pneumococcal disease differed significantly by race in this analysis, sometimes even resulting in inverse trends in white versus black children. With poverty as an example, the highest rates of disease for white children were seen in the most impoverished census tracts whereas the highest rates of disease for black children were seen in the least impoverished census tracts. Despite these differences, black children consistently had higher rates of disease compared to white children within the same socioeconomic strata. Because the direction of the association between socioeconomic variables and the rate of invasive pneumococcal disease differed by race, future studies examining the reason for the relationship between socioeconomic factors and disease rates should consider stratifying on race.

The results seen among black children in this analysis were unexpected. Among black children, worse socioeconomic conditions were associated with lower rates of invasive pneumococcal disease. High percentages of census tract poverty and household crowding resulted in significantly lower rates of invasive pneumococcal disease whereas census tracts with high median household income had higher rates of disease. These unexpected results likely indicate the presence of an unmeasured confounder in the black population. Access to or utilization of healthcare could potentially explain these results.

Vaccination status is one aspect of healthcare utilization that was available in the dataset. When results were stratified on vaccination status, the association between socioeconomic variables and invasive pneumococcal disease differed substantially for vaccinated and unvaccinated populations. For example, in vaccinated populations crowding was associated with lower rates of disease whereas in unvaccinated populations crowding was associated with higher rates of disease. These results demonstrate that socioeconomic factors are probably more important predictors of disease for unvaccinated individuals.

Interestingly, high crowding appears to be associated with lower rates of invasive pneumococcal disease among vaccinated individuals. One possible explanation for that observation relates to differences in healthcare practice. Free clinics tend to be prevalent in impoverished, crowded areas. Sick children living in these areas who visit the free clinics may receive empiric antibiotic treatment for infections rather than blood cultures and other costly diagnostic tests. Therefore, those children are less likely to be diagnosed with invasive pneumococcal disease because they receive fewer diagnostic tests than their wealthier counterparts. Children living in less impoverished, crowded areas may visit emergency rooms or private pediatric offices that are more likely to use diagnostic tests like blood cultures, which results in a higher detection of invasive pneumococcal disease in these areas.

Although the inverse association of invasive pneumococcal disease with crowding and poverty has not been previously observed in children in the United States, a similar association has been observed in other populations. A study of invasive *Haemophilus influenzae* in Europe observed that rates of disease decreased as population density increased (48). Further research should be done to better define the reason behind this unexpected association.

Strengths and Limitations

This was the first study to examine the race-specific effect of socioeconomic measures on rates of invasive pneumococcal disease in children. This study had multiple strengths. First, the effect of multiple socioeconomic measures was examined rather than just using income to define socioeconomic status. Socioeconomic factors are not interchangeable, so it is important to examine the effect of multiple different variables after considering potential mechanistic explanations for their association with the disease of interest (46). Second, socioeconomic variables were examined as exposures rather than just using them to control for potential confounders. Third, the surveillance region and the cases contained a high percentage of both black and white individuals allowing for sufficient examination of race-specific effects of socioeconomic factors on disease rates.

This study also had several notable limitations. First, this study only examined 905 cases, which was not as large of a sample size as in other studies, especially considering that this study stratified on race. Second, although a significant difference in invasive pneumococcal disease rate existed between white race and "other" race, no valid conclusions were possible regarding individuals of "other" race because of the heterogeneity of that racial group. Because of the small number of individuals of Asian, Native American/Alaskan, and Hawaiian/Pacific Islander descent, all of those cases had to be combined into one racial category. This heterogeneous collection likely did not accurately represent the association between socioeconomic factors and invasive pneumococcal disease rates in all of those races. Third, because census tract-level data was only available from the decennial census, all socioeconomic variables and population denominators were obtained from the 2000 census, which likely overestimated disease rates and may have resulted in misclassification of socioeconomic status for cases in later years. Fourth, because population denominators were not available for PCV7 vaccination rates and underlying disease rates, the final models were unable to control for those factors and were limited to stratified analyses. Lastly, area-based socioeconomic measures are not proxies for individual-level socioeconomic status, so it is possible that significant associations exist between socioeconomic factors and invasive pneumococcal disease rates in children even though they were not observed in this study.

Public Health Implications and Future Directions

This study defined socioeconomic disparities in invasive pneumococcal disease in children less than five years of age, which was listed as an objective for *Health People 2020* (6, 8). The socioeconomic health disparities identified in this study can be monitored over time and used to direct prevention efforts at the appropriate populations. The effect of socioeconomic measures appears to vary by race, so public health surveillance reports should analyze changes in disease rates stratified by race and socioeconomic factors.

Future research should focus on identifying the mechanisms through which socioeconomic factors affect invasive pneumococcal disease rates in children. This study identified socioeconomic health disparities in children, but further studies should see if this relationship is observed in other U.S. populations. Individual-level socioeconomic data should also be collected to identify whether the relationship between individual-level socioeconomic measures and disease rates are the same as for area-based measures. Studies examining qualitative information for each socioeconomic factor, such as quality of health education, should also be examined to identify specific mechanisms through which these socioeconomic factors affect invasive pneumococcal disease rates. By identifying the mechanisms behind the association between socioeconomic factors and invasive pneumococcal disease, public health programs can be implemented to reduce those disparities. Lastly, since area-based measures do not appear to account for racial disparities in invasive pneumococcal disease rates in children, it is important to continue to identify potential mechanisms explaining racial disparities so that public health interventions can be created to decrease those racial disparities.

REFERENCES

1. O'Brien KL, Wolfson LJ, Watt JP, et al. Burden of disease caused by Streptococcus pneumoniae in children younger than 5 years: global estimates. *Lancet* 2009;374(9693):893-902.
2. Huang SS, Johnson KM, Ray GT, et al. Healthcare utilization and cost of pneumococcal disease in the United States. *Vaccine* 2011;29(18):3398-412.
3. Butler JC, Breiman RF, Campbell JF, et al. Pneumococcal polysaccharide vaccine efficacy. An evaluation of current recommendations. *JAMA* 1993;270(15):1826-31.
4. Butler JC, Schuchat A. Epidemiology of pneumococcal infections in the elderly. *Drugs Aging* 1999;15 Suppl 1:11-9.
5. Whitney CG, Farley MM, Hadler J, et al. Decline in invasive pneumococcal disease after the introduction of protein-polysaccharide conjugate vaccine. *N Engl J Med* 2003;348(18):1737-46.
6. Health People 2020. Washington, DC: U.S. Department of Health and Human Services. Office of Disease Prevention and Health Promotion. (http://www.healthypeople.gov/2020/topicsobjectives2020/pdfs/HP2020objectives.pdf). (Accessed 11/02/2011).
7. Healthy People 2010. Immunization and infectious diseases. Washington, D.C.: Department of Health and Human Services. Office of Disease Prevention and Health Promotion. (http://www.healthypeople.gov/2010/document/HTML/Volume1/14Immunization.htm). (Accessed 11/02/2011).
8. Healthy People 2020: Social Determinants of Health. Washington, D.C.: Department of Health and Human Services. (http://www.healthypeople.gov/2020/topicsobjectives2020/overview.aspx?topicid=39). (Accessed 11/02/2011).
9. Albrich WC, Baughman W, Schmotzer B, et al. Changing characteristics of invasive pneumococcal disease in Metropolitan Atlanta, Georgia, after introduction of a 7-valent pneumococcal conjugate vaccine. *Clin Infect Dis* 2007;44(12):1569-76.
10. Hsu K, Pelton S, Karumuri S, et al. Population-based surveillance for childhood invasive pneumococcal disease in the era of conjugate vaccine. *Pediatr Infect Dis J* 2005;24(1):17-23.
11. Nuorti JP, Martin SW, Smith PJ, et al. Uptake of pneumococcal conjugate vaccine among children in the 1998-2002 United States birth cohorts. *Am J Prev Med* 2008;34(1):46-53.
12. Tasslimi A, Wenger P, Pentakota SR, et al. Invasive pneumococcal disease in an underimmunized, high HIV prevalence population. *J Infect* 2008;56(2):99-102.
13. Active Bacterial Core Surveillance, Emerging Infections Program Network, Streptococcus pneumoniae, 1999. Centers for Disease Control and Prevention; 2000. (http://www.cdc.gov/abcs/reports-findings/survreports/spneu99.html). (Accessed 11/02/2011).
14. Active bacterial Core Surveillance Report, Emerging Infections Program Network, Streptococcus pneumoniae, 2010. Centers for Disease Control and

Prevention; 2011. (http://www.cdc.gov/abcs/reports-findings/survreports/spneu10.html). (Accessed 11/02/2011).

15. National, state, and local area vaccination coverage among children aged 19-35 months--United States, 2006. *MMWR Morb Mortal Wkly Rep* 2007;56(34):880-5.
16. Wooten KG, Luman ET, Barker LE. Socioeconomic factors and persistent racial disparities in childhood vaccination. *Am J Health Behav* 2007;31(4):434-45.
17. Hjuler T, Wohlfahrt J, Staum Kaltoft M, et al. Risks of invasive pneumococcal disease in children with underlying chronic diseases. *Pediatrics* 2008;122(1):e26-32.
18. Pilishvili T, Zell ER, Farley MM, et al. Risk factors for invasive pneumococcal disease in children in the era of conjugate vaccine use. *Pediatrics* 2010;126(1):e9-17.
19. Burton DC, Flannery B, Bennett NM, et al. Socioeconomic and racial/ethnic disparities in the incidence of bacteremic pneumonia among US adults. *Am J Public Health* 2010;100(10):1904-11.
20. Flory JH, Joffe M, Fishman NO, et al. Socioeconomic risk factors for bacteraemic pneumococcal pneumonia in adults. *Epidemiol Infect* 2009;137(5):717-26.
21. Nuorti JP, Butler JC, Gelling L, et al. Epidemiologic relation between HIV and invasive pneumococcal disease in San Francisco County, California. *Ann Intern Med* 2000;132(3):182-90.
22. Schuchat A, Broome CV, Hightower A, et al. Use of surveillance for invasive pneumococcal disease to estimate the size of the immunosuppressed HIV-infected population. *JAMA* 1991;265(24):3275-9.
23. Davidson M, Parkinson AJ, Bulkow LR, et al. The epidemiology of invasive pneumococcal disease in Alaska, 1986-1990--ethnic differences and opportunities for prevention. *J Infect Dis* 1994;170(2):368-76.
24. Cortese MM, Wolff M, Almeido-Hill J, et al. High incidence rates of invasive pneumococcal disease in the White Mountain Apache population. *Arch Intern Med* 1992;152(11):2277-82.
25. Bennett NM, Buffington J, LaForce FM. Pneumococcal bacteremia in Monroe County, New York. *Am J Public Health* 1992;82(11):1513-6.
26. Harrison LH, Dwyer DM, Billmann L, et al. Invasive pneumococcal infection in Baltimore, Md: implications for immunization policy. *Arch Intern Med* 2000;160(1):89-94.
27. Pastor P, Medley F, Murphy TV. Invasive pneumococcal disease in Dallas County, Texas: results from population-based surveillance in 1995. *Clin Infect Dis* 1998;26(3):590-5.
28. Poehling KA, Talbot TR, Griffin MR, et al. Invasive pneumococcal disease among infants before and after introduction of pneumococcal conjugate vaccine. *JAMA* 2006;295(14):1668-74.
29. Soto K, Petit S, Hadler JL. Changing disparities in invasive pneumococcal disease by socioeconomic status and race/ ethnicity in Connecticut, 1998-2008. *Public Health Rep* 2011;126 Suppl 3:81-8.
30. Flannery B, Schrag S, Bennett NM, et al. Impact of childhood vaccination on racial disparities in invasive Streptococcus pneumoniae infections. *JAMA* 2004;291(18):2197-203.

31. Talbot TR, Poehling KA, Hartert TV, et al. Elimination of racial differences in invasive pneumococcal disease in young children after introduction of the conjugate pneumococcal vaccine. *Pediatr Infect Dis J* 2004;23(8):726-31.
32. Du P, McNutt LA, O'Campo P, et al. Changes in community socioeconomic status and racial distribution associated with gonorrhea rates: an analysis at the community level. *Sex Transm Dis* 2009;36(7):430-8.
33. Krieger N, Waterman PD, Chen JT, et al. Monitoring socioeconomic inequalities in sexually transmitted infections, tuberculosis, and violence: geocoding and choice of area-based socioeconomic measures--the public health disparities geocoding project (US). *Public Health Rep* 2003;118(3):240-60.
34. Yousey-Hindes KM, Hadler JL. Neighborhood socioeconomic status and influenza hospitalizations among children: New Haven County, Connecticut, 2003-2010. *Am J Public Health* 2011;101(9):1785-9.
35. Krieger N, Chen JT, Waterman PD, et al. Choosing area based socioeconomic measures to monitor social inequalities in low birth weight and childhood lead poisoning: The Public Health Disparities Geocoding Project (US). *J Epidemiol Community Health* 2003;57(3):186-99.
36. Krieger N, Chen JT, Waterman PD, et al. Geocoding and monitoring of US socioeconomic inequalities in mortality and cancer incidence: does the choice of area-based measure and geographic level matter?: the Public Health Disparities Geocoding Project. *Am J Epidemiol* 2002;156(5):471-82.
37. Krieger N, Williams DR, Moss NE. Measuring social class in US public health research: concepts, methodologies, and guidelines. *Annu Rev Public Health* 1997;18:341-78.
38. Geographic Areas Reference Manual. U.S Census Bureau. (http://www.census.gov/geo/www/garm.html). (Accessed 11/02/2011).
39. Krieger N, Chen JT, Waterman PD, et al. Race/ethnicity, gender, and monitoring socioeconomic gradients in health: a comparison of area-based socioeconomic measures--the public health disparities geocoding project. *Am J Public Health* 2003;93(10):1655-71.
40. Diez-Roux AV, Kiefe CI, Jacobs DR, Jr., et al. Area characteristics and individual-level socioeconomic position indicators in three population-based epidemiologic studies. *Ann Epidemiol* 2001;11(6):395-405.
41. Breiman RF, Spika JS, Navarro VJ, et al. Pneumococcal bacteremia in Charleston County, South Carolina. A decade later. *Arch Intern Med* 1990;150(7):1401-5.
42. Chen FM, Breiman RF, Farley M, et al. Geocoding and linking data from population-based surveillance and the US Census to evaluate the impact of median household income on the epidemiology of invasive Streptococcus pneumoniae infections. *Am J Epidemiol* 1998;148(12):1212-8.
43. Dagan R, Gradstein S, Belmaker I, et al. An outbreak of Streptococcus pneumoniae serotype 1 in a closed community in southern Israel. *Clin Infect Dis* 2000;30(2):319-21.
44. Gratten M, Morey F, Dixon J, et al. An outbreak of serotype 1 Streptococcus pneumoniae infection in central Australia. *Med J Aust* 1993;158(5):340-2.

45. Romney MG, Hull MW, Gustafson R, et al. Large community outbreak of Streptococcus pneumoniae serotype 5 invasive infection in an impoverished, urban population. *Clin Infect Dis* 2008;47(6):768-74.
46. Braveman PA, Cubbin C, Egerter S, et al. Socioeconomic status in health research: one size does not fit all. *JAMA* 2005;294(22):2879-88.
47. Levine OS, Farley M, Harrison LH, et al. Risk factors for invasive pneumococcal disease in children: a population-based case-control study in North America. *Pediatrics* 1999;103(3):E28.
48. Olowokure B, Spencer NJ, Hawker JI, et al. Invasive Haemophilus influenzae disease: an ecological study of sociodemographic risk factors before and after the introduction of Hib conjugate vaccine. *Eur J Epidemiol* 2003;18(4):363-7.
49. United States Census Bureau. US Census 2000. (http://www.factfinder.census.gov). (Accessed 6/12/2011).