Changing Characteristics of Invasive Pneumococcal Disease in Metropolitan Atlanta, Georgia, after Introduction of a 7-Valent Pneumococcal Conjugate Vaccine

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Background. The rate of invasive pneumococcal disease (IPD) has decreased among both immunized children and nonimmunized adults since the licensure of a heptavalent pneumococcal conjugate vaccine (PCV7) for use in infants in the United States in 2000.

Methods. Temporal trends in IPD incidence, clinical syndromes, and underlying conditions were analyzed using active laboratory- and population-based surveillance data from the Centers for Disease Control and Prevention–sponsored Georgia Emerging Infections Program for the 20-county Metropolitan Atlanta, Georgia, for the period of July 1997 through June 2004. P values were determined by test for trend.

Results. Since 2000, there have been significant decreases in the rates of invasive pneumococcal pneumonia (relative risk [RR], 0.80; P < .002) and meningitis (RR, 0.41; P = .003) in adults and for primary bacteremia, invasive pneumonia, and meningitis in children (RR, 0.16 [P < .001], 0.60 [P = .003], and 0.70 [P = .009], respectively). Among human immunodeficiency virus–infected persons, there were significant decreases in the overall rates of IPD (decrease of 43%; P < .001) and invasive pneumonia (decrease of 44%; P < .001) since 2000–2001, although the rate of IPD increased significantly (increase of 53%; P = .022) among patients with acquired immunodeficiency syndrome. There was a concurrent increase in the proportion of adults aged ≥40 years with underlying comorbidities. Rates of non-PCV7 serotypes increased 1.61-fold and 1.28-fold from 2000–2001 to 2003–2004 in children and adults (P = .005 for both).

Conclusions. The decreasing incidence of IPD in Atlanta since 2000–2001 was associated with decreases in cases of pneumonia and meningitis in adult and pediatric subjects and in cases of primary bacteremia in children. The burden of serotype-replacement disease remained small. Adults with comorbidities represent a growing proportion of patients with IPD.

Streptococcus pneumoniae is a major cause of localized respiratory tract infection and serious invasive disease worldwide in both children and adults [1, 2]. Despite the availability of appropriate antibiotic therapy, pneumococcal disease is associated with considerable morbidity and mortality. Individuals at the extremes of age and in certain ethnic groups, such as black persons, American Indians, and Alaska Natives, are disproportionately affected [3–5]. Other risk factors for invasive pneumococcal disease (IPD) include smoking, HIV infection/AIDS, organ transplantation, alcoholism, diabetes mellitus, renal dysfunction, and sickle cell disease [3, 6].

In February 2000, a 7-valent pneumococcal conjugate vaccine (PCV7; Prevnar, Wyeth) was approved in the United States for use in children aged <2 years and in children with high-risk conditions who are aged <5 years. PCV7 was included in the routine immunization schedule in mid-2000. PCV7 targets the pneumococcal serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F, which were
responsible for >80% of cases of IPD cases in children before the introduction of the vaccine. In addition to a direct reduction in the incidence of IPD among persons in the vaccinated age groups, the introduction of PCV7 has prevented more than twice as many cases of IPD due to PCV7 serotypes in persons from unvaccinated age groups through indirect herd immunity [7].

The introduction of PCV7 has led to concerns about serotype replacement by non-PCV7 strains and the potential for capsular switching, which may result in reemergence of antibiotic resistance in non-PCV7 serotypes [8, 9]. Newer-generation pneumococcal conjugate vaccines with extended serotype coverage are being developed to meet these ongoing challenges.

Most studies assessing the influence of PCV7 have thus far focused primarily on children or on populations with specific risk factors. The purpose of this study was to assess changes in pneumococcal serotype distribution, clinical syndromes, and underlying diseases associated with IPD since the introduction of vaccination with PCV7 in Metropolitan Atlanta, Georgia.

METHODS

Identification of cases of IPD. Active, population-based laboratory surveillance for all *S. pneumoniae* isolates recovered from normally sterile body sites in residents of the 20-county Metropolitan Atlanta area was conducted during the period from 1 July 1997 through 30 June 2004 as part of the Centers for Disease Control and Prevention (CDC)–sponsored Active Bacterial Core Surveillance of the Georgia Emerging Infections Program [10, 11]. Isolates were serotyped at the CDC (Atlanta) using the Quellung reaction. Clinical laboratory records were audited monthly to assure completeness of reporting. Medical records were reviewed for underlying diseases and clinical manifestations of IPD for all pneumococcal cases in the 20-county Metropolitan Atlanta area since 1 January 2000. Primary bacteremia (hereafter, “bacteremia”) was defined as isolation of *S. pneumoniae* from ≥1 blood culture without a defined source of infection.

Population data. Our study used US Census Bureau data for calendar year 2000 and postcensus population estimates for the remaining years. Data for persons living with AIDS were obtained from the Georgia Department of Human Resources, Division of Public Health, Epidemiology Branch, HIV/STD Epidemiology Section, HIV Surveillance Unit. AIDS (not HIV infection) was reportable in Georgia during the study period. According to previous reports, approximately two-thirds of all living and recognized HIV-infected patients have received a diagnosis of AIDS at some point [12]. Therefore, the number of persons with HIV infection was calculated as follows: the number of HIV-infected persons = the number of persons with AIDS × 1.5. The prevalence of asthma in Georgia was determined on the basis of self-reported data [13]. Data on the prevalence of diabetes mellitus in Georgia was obtained from the CDC’s Diabetes Program [14].

Classification of pneumococcal serotypes. Serotype distribution was categorized as follows: PCV7 serotypes were 4, 6B, 9V, 14, 18C, 19F, and 23F; PCV13 serotypes, which represented serotypes included in an investigational vaccine (Wyeth) [15], were all PCV7 serotypes plus 1, 3, 5, 6A, 7F, and 19A. Non-PCV7 serotypes were all serotypes not included in PCV7. PCV7-related serotypes were 6A, 9A, 9N, 18A, 18B, 18F, 19A, 23A, and 23B. Serotype-specific rates were calculated by assuming that cases with missing isolates had the same serotype distribution as those with known serotypes.

Time periods. Cases that occurred during the period from 1 July 1997 through 30 June 2004 were evaluated. The “respiratory season” was defined as the period from 1 July through 30 June of the following year. The “prevaccine period” was defined as the period from 1 July 1997 through 30 June 2000, and the “postvaccine period” was defined as the period from 1 July 2000 through 30 June 2004.

Statistical analysis. Data analysis was performed using SAS software, version 9.1 (SAS Institute), and Epi Info 2002 (CDC). Rates for respiratory seasons and for pre-versus postvaccine periods were calculated using census population data. The Cochran-Armitage χ² test for trend was used for analysis of trends over time. Mean values for continuous variables were compared using 2-sided pooled t tests. Proportions were compared using Pearson’s χ² test or Fisher’s exact test, as appropriate. P values ≤.05 were considered to be statistically significant.

Multivariable analysis. The number of IPD cases, as the primary outcome measure, was directly obtained from the surveillance database. The number of “non-IPD” cases was indirectly calculated by subtracting the number of IPD cases from the number of persons at risk in the respective categories. Time period relative to introduction of PCV7 in mid-2000 was the exposure variable, with a relative risk (RR) of <1 for time indicating a lower risk of IPD after introduction of the vaccine. Covariates were patient sex, age, and race. Unconditional logistic regression with hierarchical backward selection was performed with a required level of significance of .10 to remain in the model. Two-way interactions were entered into the model, and they remained if they were significant at α = .05. Models were compared using the likelihood ratio test. Goodness of fit was determined using the Hosmer and Lemeshow test.

RESULTS

IPD. During the pre- and postvaccine periods, 3096 and 2638 cases of IPD were identified, respectively. The mean age of patients with IPD increased significantly in the postvaccine period, primarily because of a 42% reduction in the proportion of all cases of IPD occurring in children. The sex and race
distribution of cases remained unchanged. White and black patients predominated (table 1).

Compared with the prevaccine period, rates of IPD decreased significantly in all age groups (except among persons aged 5–17 years), in both sexes, and in all races in the postvaccine period (table 1). Compared with the 1999–2000 season, during the 2003–2004 season, there was a 75% decrease in the overall rate of IPD among children aged <18 years and a 26.6% decrease for adults (P < .001 for both comparisons). The protective effect of the time after introduction of vaccine on the rate of IPD differed between children and adults and between white and black persons, with the greatest protection noted for black children (RR, 0.31) and the smallest protection noted for white adults (RR, 0.76). In multivariable analysis restricted to adults, the significant risk factors associated with IPD were male sex, age > 65 years, and black race, whereas Asian race was found to be protective (table 2).

Clinical syndromes. Bacteremia (49%) was the most common clinical syndrome among children after the introduction of PCV7, followed by pneumonia (23%) and otitis media (12%). In adults, pneumonia represented 70% of IPD cases in the period after July 2000, followed by bacteremia (17%) and meningitis (6%). The rate of pneumonia was 3.07-fold (95% CI, 2.62–3.59-fold) higher in adults than in children, whereas rates of bacteremia, meningitis, and otitis were lower in adults (RR, 0.35, 0.68, and 0.10, respectively; P < .001). Chart reviews for clinical syndromes were not performed before 1 January 2000.

Among adults, from 2000–2001 to 2003–2004, there was a 30% decrease in the rate of bacteremia (95% CI, 5%–48%), a 58% decrease in the rate of meningitis (95% CI, 28%–76%), and a 20% decrease in the rate of pneumonia (95% CI, 8%–31%) (figure 1). For the period after 2000, Cochran-Armitage $\chi^2$ tests for trend revealed that the decreasing rates of pneum-

Table 1. Rates among and demographic characteristics of patients with invasive pneumococcal disease (IPD) for periods before and after the introduction of 7-valent pneumococcal conjugate vaccine.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Percentage of subjects with IPD</th>
<th>Rate of IPD per 100,000 persons per year</th>
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|               | Prevaccine period | Postvaccine period | RR (95% CI) | P
| Age ≤4 years | 38.5 | 22.3 | 139.73 | 44.11 | 0.32 (0.29–0.35) | <.001 |
| 5–17 years    | 2.6 | 4.1 | 3.93 | 3.30 | 0.84 (0.63–1.12) | .23 |
| 18–39 years  | 15.7 | 16.0 | 11.74 | 6.89 | 0.59 (0.51–0.67) | <.001 |
| 40–64 years  | 24.6 | 33.9 | 22.95 | 17.22 | 0.75 (0.69–0.83) | <.001 |
| >65 years    | 18.6 | 23.7 | 65.42 | 48.18 | 0.74 (0.66–0.82) | <.001 |

Table 2. Risk factors for invasive pneumococcal disease in adults in multivariable analysis (model without interaction terms).

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>RR (95% CI)</th>
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<tbody>
<tr>
<td>Age, &gt;65 vs. 18–64 years</td>
<td>4.58 (4.27–4.92)</td>
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<tr>
<td>Male sex</td>
<td>1.35 (1.26–1.44)</td>
</tr>
<tr>
<td>Black vs. white race</td>
<td>2.44 (2.28–2.61)</td>
</tr>
<tr>
<td>American Indian vs. white race</td>
<td>0.41 (0.13–1.27)</td>
</tr>
<tr>
<td>Asian/Pacific Islander vs. white race</td>
<td>0.16 (0.10–0.28)</td>
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| Time after introduction of childhood vaccination vs. time before introduction of childhood vaccination | 0.71 (0.66–0.75)

NOTE. The prevaccine period was from 1 July 1997 through 30 June 2000, and the postvaccine period was from 1 July 2000 through 30 June 2004. RR, relative risk.

a Determined using the $\chi^2$ test (a = .05).
monia ($P<.001$) and meningitis ($P = .003$) were significant, but this was not true for bacteremia ($P = .12$).

In a comparison of the 2003–2004 and 2000–2001 seasons, among children, there was a 69% decrease in the rate of bacteremia (95% CI, 58%–77%), a 63% decrease in the rate of meningitis (95% CI, 24%–82%), and a 42% decrease in the rate of pneumonia (95% CI, 15%–61%) (figure 1). For the period after 2000, $\chi^2$ tests for trend indicated that the decreases for these 3 syndromes in children were significant ($P<.001$, $P = .009$, and $P = .003$, respectively).

In a comparison of the 2003–2004 and 2000–2001 seasons, among HIV-infected patients, there were significant decreases in the annual rate of IDP (−43%), largely as a result of decreases in the rate of pneumonia (−44%; $P<.001$ for both, by $\chi^2$ test for trend). Simultaneously, in the subset of patients with AIDS, the overall rate of IDP significantly increased (+53%; $P = .021$, by $\chi^2$ test for trend); this was particularly the case for pneumonia (+56%; $P = .059$, by $\chi^2$ test for trend) (figure 2 and table 3). In patients with AIDS, the rates of IDP, pneumonia, and bacteremia were 51%, 51% (both $P<.001$ for both), and 48% ($P = .01$) lower than the rates in all HIV-infected individuals. The rate of meningitis did not differ between these 2 groups ($P = .73$).

**Serotype distribution.** There was no significant year-to-year variability observed in the proportion of IDP cases due to serotypes covered by PCV7 among children (81%–84% of cases) and adults (53%–62% of cases) during the prevaccine period, but the proportion decreased significantly after the introduction of PCV7 (95% CI, 24%–82%) during the prevaccine period, but the proportion decreased significantly after the introduction of PCV7 ($P<.001$ for children and adults). In 2003–2004, PCV7 coverage was 16% of pediatric IDP cases and 26% of adult IDP cases; PCV13 would cover 29% and 39%, respectively.

Significant downward trends in the rate of IDP due to PCV7 serotypes were noted for all age groups after the introduction
of PCV7 (figure 3A). During the 2003–2004 season, there was a 96% decrease in the rate of IPD due to PCV7 serotypes for children aged <5 years, and there was a 68%–72% reduction for adult age groups, compared with the prevaccine period (P < .001 for all comparisons).

From 2000–2001 through 2003–2004, there were small—but significant—upward trends in the rates of IPD caused by non-PCV7 serotypes among children (P < .001) and adults (P = .004) (figure 3B). The rates of IPD due to non-PCV7 serotypes in children and adults were 1.61-fold (95% CI, 1.15–2.26-fold) and 1.28-fold (95% CI, 1.08–1.51-fold; P = .005 for both) higher in 2003–2004 than in 2000–2001.

For the postvaccine period versus the prevaccine period, the rate of vaccine-related IPD due to serotype 19A increased significantly for children and adults (P < .01 for both), accounting for much of the increase in non-PCV7 serotype cases of IPD (figure 3C). These increases were most notable for subjects aged ≤4 years (prevaccine vs. postvaccine periods, 2.8 vs. 5.8 cases per 100,000 persons; RR, 2.05; 95% CI, 1.21–3.46; P < .01) and 40–64 years (prevaccine vs. postvaccine periods, 0.8 vs. 1.4 cases per 100,000 persons; RR, 1.81; 95% CI, 1.13–2.92; P < .02). In contrast, the combined rates for all other PCV7-related serotypes decreased significantly for children (P < .001) and nonsignificantly for adults (P = .35).

**Underlying conditions.** Since 2000–2001, there has been an increase in the proportion of patients with IPD aged ≥40 years who have comorbidities (P = .004). The proportions of adults with IPD and AIDS, diabetes mellitus, liver cirrhosis or failure, and/or asthma increased from 2000–2001 to 2003–2004, whereas the proportion of patients with IPD and HIV infection (with or without AIDS) remained unchanged (table 3). No significant changes over time in the rates of IPD were observed for patients with asthma or diabetes.

**DISCUSSION**

This population-based study from Metropolitan Atlanta confirmed reports of a reduced burden of IPD among children and adults in various areas in the United States since the introduction of PCV7 [7, 10, 16–18], and of an extension of the beneficial effects to nonvaccinated adults [19]. Rates of IPD were significantly lower after the introduction of PCV7 than during the prevaccine period. Black race and male sex are known risk factors for IPD [6], whereas the reduced risk among Asian subjects was a new finding. Although we were able to control only for a limited number of risk factors for IPD, additional evidence of a causative role of PCV7 as the driving factor for this reduction is available. The largest reduction in the rate of IPD occurred in the target population for PCV7, and it was primarily due to a decrease in the rate of PCV7

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**Table 3. Comorbidities among persons aged ≥18 years with invasive pneumococcal disease (IPD).**

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<tr>
<td><strong>Asthma</strong></td>
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<tr>
<td>No. (%) of patients with IPD and asthma</td>
<td>31 (5.5)</td>
<td>27 (5.9)</td>
<td>19 (4.4)</td>
<td>46 (9.4)</td>
<td>.033</td>
</tr>
<tr>
<td>No. of IPD cases per 100,000 patients</td>
<td>16.6</td>
<td>12.0</td>
<td>8.0</td>
<td>20.1</td>
<td>.46</td>
</tr>
<tr>
<td><strong>Diabetes mellitus</strong></td>
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<tr>
<td>No. (%) of patients with IPD and diabetes mellitus</td>
<td>78 (13.8)</td>
<td>64 (14.0)</td>
<td>84 (19.3)</td>
<td>86 (17.7)</td>
<td>.024</td>
</tr>
<tr>
<td>No. of IPD cases per 100,000 patients with diabetes mellitus</td>
<td>38.6</td>
<td>28.3</td>
<td>34.4</td>
<td>33.3</td>
<td>.63</td>
</tr>
<tr>
<td><strong>HIV infection</strong></td>
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<tr>
<td>No. (%) of patients with IPD and HIV infection</td>
<td>100 (19.2)</td>
<td>81 (18.2)</td>
<td>84 (20.0)</td>
<td>76 (16.4)</td>
<td>.39</td>
</tr>
<tr>
<td>No. of IPD cases per 100,000 patients with HIV infection</td>
<td>958.0</td>
<td>645.6</td>
<td>613.4</td>
<td>548.2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>AIDS</strong></td>
<td></td>
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<tr>
<td>No. (%) of patients with IPD and AIDS</td>
<td>23 (4.1)</td>
<td>18 (3.9)</td>
<td>32 (7.4)</td>
<td>44 (9.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>No. of IPD cases per 100,000 patients with AIDS</td>
<td>295.1</td>
<td>212.6</td>
<td>350.5</td>
<td>452.3</td>
<td>.021</td>
</tr>
<tr>
<td>No. (%) of patients with IPD and liver cirrhosis</td>
<td>9 (1.6)</td>
<td>16 (3.5)</td>
<td>11 (2.5)</td>
<td>21 (4.3)</td>
<td>.025</td>
</tr>
<tr>
<td>No. of IPD cases per 100,000 patients with liver cirrhosis</td>
<td>433 (85.9)</td>
<td>363 (88.5)</td>
<td>376 (92.8)</td>
<td>386 (88.5)</td>
<td>.058</td>
</tr>
</tbody>
</table>
| **NOTE.** Shown are minimum proportions of underlying diseases in adult cases of IPD. No denominators were available for patients with liver cirrhosis and "any disease." Data on current asthma and diabetes mellitus were available only for the whole state of Georgia and were extrapolated to the 20-county Metropolitan Atlanta area.  
* Determined using Cochran-Armitage \( \chi^2 \) test (\( \alpha = .05 \)).  
** Includes asplenia or status after splenectomy, asthma, emphysema or chronic obstructive pulmonary disease, diabetes mellitus, HIV infection, AIDS, sickle cell disease, Hodgkin disease, leukemia, multiple myeloma, any other malignancy, immunoglobulin deficiency, receipt of immunosuppressive therapy (including corticosteroids, chemotherapy, and radiation), organ transplantation, systemic lupus erythematosus, liver failure or cirrhosis, nephrotic syndrome, renal failure or receipt of dialysis, cardiovascular or cerebrovascular disease, heart failure, CSF leak, burns, alcohol abuse, injection drug use, and other illnesses.

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Clinical Trends of Pneumococcal Disease • CID 2007:44 (15 June) • 1573
Figure 3. Incidence rates of invasive pneumococcal disease, by year and age group, compared with the prevaccine period (1 July 1997 through 30 June 2000). Each respiratory season is defined as the period from 1 July of one year through 30 June of the following year. A, Rates of invasive pneumococcal disease due to PCV7 serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F). All data points represent significant decreases (P < .05) from rates during the prevaccine years, except for the years 2000–2001, 2001–2002, and 2002–2003 for children aged 5–17 years and for 2000–2001 for adults aged 40–64 years and ≥65 years. B, Rates of invasive pneumococcal disease due to non-PCV7 serotypes (i.e., all serotypes not included in the PCV7). *P < .05, compared with prevaccine years. C, Rates of invasive pneumococcal disease due to serotype 19A. *P < .05, compared with prevaccine years.
rates [29, 30] but higher than US data from 1999–2000 (423 cases per 100,000 persons) [31]. Differences in these rates may, in part, be explained by our method of calculating the number of HIV-infected individuals on the basis of the number of reported cases of AIDS [12] or by differences in other demographic characteristics of HIV-infected individuals in our surveillance area. Receipt of antiretroviral therapy and prior 23PPV vaccination when the CD4 cell count is ≥500 cells/μL are associated with protection from IPD in HIV-infected persons [32]. Although we had no data on CD4 cell counts or receipt of antibiotics, antiretroviral medications, or 23PPV in our study population, a possible explanation for the lower rate of IPD among persons with AIDS than among all HIV-infected persons is immune reconstitution after antiretroviral therapy. However, we have observed an increasing proportion of cases of AIDS as an underlying disease since 2000–2001, whereas the overall proportion of persons with HIV infection has remained unchanged. We speculate that patients with AIDS may benefit less from herd immunity and may be more susceptible to emerging serotypes, compared with HIV-infected persons without AIDS. The relatively small size of IPD subgroups for patients with HIV infection or AIDS possibly limits this analysis.

This investigation confirmed the findings of a previous report about increasing proportions of patients with IPD who have comorbidities [17]. It is important to note that, for asthma and diabetes, this seems to be largely associated with increasing prevalences of these 2 conditions in the general population. Unfortunately, because of a lack of prevalence data, this correlation could not be assessed for other underlying diseases. Assessment of trends for some comorbidities (such as liver cirrhosis), even though these comorbidities were represented in proportions similar to previous reports [6], was limited by relatively small numbers. It was previously suggested that there may be differential susceptibility for patients with chronic underlying conditions to the non-PCV7 serotypes prevalent after the introduction of PCV7, leading to a disproportionate risk of IPD [17]. Clearly, additional efforts are warranted to better protect at-risk adult populations by reinforcing current vaccination strategies and evaluating new ones [33–35].

Serotype replacement poses future challenges to improved prevention of pneumococcal disease. Importantly, the burden of serotype replacement disease in our population was small, compared with the large burden of pneumococcal disease prevented due to PCV7. At our site, as at other sites across the United States, a number of vaccine-related and other non-PCV7 serotypes have emerged, and several are included in candidate pneumococcal conjugate vaccines with expanded coverage (serotypes 1, 3, 5, 6A, 7, and 19A) [16, 18]. Serotype 19A has become particularly important in many areas of the United States [36] and appears to be responsible for a considerable proportion of serotype replacement–associated disease while rates of disease due to other PCV7-related serotypes are stable or decreasing.

Our multivariable analysis was limited by the lack of information on potential confounding factors, such as sociocultural and behavioral factors, contact with children, or antibiotic use [37]. The 2003 Behavioral Risk Factor Surveillance Survey reported that 60.5% of persons aged ≥65 years in Georgia remembered having received 23PPV vaccine, but it was not possible to individually link this information to patients with IPD [38]. Finally, HIV- and AIDS-specific rates of IPD may continue to change as a result of the availability of potent antiretroviral therapy, changing diagnostic practices, sociocultural factors that affect populations at risk, and changes in the proportion of persons living with HIV infection whose conditions do not meet the criteria for AIDS. Therefore, our extrapolation of IPD rates among HIV-infected persons is only a rough estimate, albeit an estimate that falls within previously reported ranges [28–32].

A particular strength of the study is the robust, active surveillance and laboratory methods that have been standardized and validated and that are being used in different geographic areas around the United States. Other strengths include the large number of IPD cases identified, which allowed for subgroup analyses, and a diverse study population, including a large, urban inner-city population with a high prevalence of HIV infection and comorbidities. Changes in the epidemiology of IPD may become apparent in these high-risk groups more rapidly than in the general population.

Introduction of PCV7 into the childhood immunization schedule has brought major benefits to persons from vaccinated and nonvaccinated age groups. Evolving changes in clinical presentation, populations at risk, and the potential for replacement disease will require careful ongoing monitoring. Introduction of pneumococcal conjugate vaccines with expanded serotype coverage and evaluation of conjugate vaccine programs targeting broader age groups may be appropriate next steps.

Acknowledgments

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