Disappearance of Vaccine-Type Invasive Pneumococcal Disease and Emergence of Serotype 19A in a Minority Population with a High Prevalence of Human Immunodeficiency Virus and Low Childhood Immunization Rates

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We analyzed the epidemiology of invasive pneumococcal disease (IPD) following introduction of pneumococcal conjugated vaccine in an urban population with a 2% human immunodeficiency virus (HIV) prevalence and history of low childhood immunization rates. We observed near-elimination of vaccine-type IPD. Substantial disease remains due to non-vaccine-type pneumococci, highlighting the need to increase pneumococcal immunization among HIV-infected adults.

Following the introduction of 7-valent pneumococcal conjugate vaccine (PCV7) in mid-2000, declines in invasive pneumococcal disease (IPD) were documented across all age groups in the United States (1, 4, 20) and in vulnerable populations (4, 7, 17). Subsequently, increases in IPD caused by nonvaccine serotypes, particularly 19A, were observed (4, 7, 8, 9, 13, 14, 17).

Newark, NJ, is a mid-sized U.S. city with a predominantly black and Hispanic population (19), a high human immunodeficiency virus (HIV)/AIDS prevalence (2%) (11), and a history of low childhood immunization rates (2). Potential PCV7-related direct and indirect effects in such populations have not been fully studied. Statewide, passive surveillance of IPD began in mid-2003. We previously described a single Newark medical center’s experience with IPD (18). In the current study, we conducted active, population-based surveillance to complement these efforts and to better understand the contemporary epidemiology of IPD in Newark, specifically, PCV7’s impact and the roles of HIV/AIDS and race/ethnicity in IPD incidence.

Multicenter, active surveillance of all Newark IPD cases was conducted from 1 December 2007 through 30 November 2008. Cases were identified at the clinical microbiology laboratories of the four major hospitals serving Newark residents. Case ascertainment was augmented by comparisons with passive reports to New Jersey’s Communicable Disease Reporting and Surveillance System. A case was defined as any Newark resident during the study period with Streptococcus pneumoniae isolated from either blood or cerebrospinal fluid (CSF).

Patient demographics and medical information were abstracted from hospital medical charts. Collected isolates were serotyped with sequential multiplex PCR molecular methods developed by the Centers for Disease Control and Prevention (3, 12). DNA sequencing was used for resolution of serotypes 6A, 6B, and 6C. Vaccine serotypes (VT) were defined as those included in PCV7: 4, 6B, 9V, 14, 18C, 19F, and 23F. All others, including vaccine-related serotypes, were defined as nonvaccine serotypes (NVT). We separately considered the additional serotypes included in the 10- and 13-valent vaccines currently under development (6, 21).

Race/ethnicity was dichotomized as black, not Hispanic (abbreviated as “black”) versus “all others.” The “all others” category included “Hispanic, all races,” “not Hispanic, white,” “not Hispanic, other,” and “unknown.” HIV status was categorized as either HIV infected or HIV uninfected/status unknown. For most incidence analyses, results are presented using the age intervals in the U.S. Census 2000 (19): 0-4, 5-9, 10-17, 18 to 44, 45 to 64, and 65 years or older. For HIV-stratified analyses, results are presented using the age intervals in Newark’s HIV/AIDS prevalence reports (11): <13, 13 to 54, and 55 years or older. The χ² test of independence and Fisher’s exact test were used, as appropriate, in univariate analyses (16).

During the study period 87 cases of IPD were identified among Newark residents. A total of 81 (93%) occurred at study centers, of which 72 (89%) were collected for serotyping and are described in detail in this report. Three isolates had no extractable DNA, and of the remaining 69, 5 were nontypeable. Ten cases that had not been reported through passive...
surveillance were identified using the study's active surveillance methods. Considering all 87 cases during the study period, the reported 1-year incidence of IPD per 100,000 in Newark was 32 (95% confidence interval [CI], 25 to 38). The age distribution was bimodal with peaks in the under-5-years age group and the 45- to 64-years age group (Fig. 1). Considering the 72 cases for which full data were available, the relative risk (RR) of IPD for black cases versus all other cases was 2.2 (95% CI, 1.4 to 3.7) and was highest among persons 18 to 44 years old (6.4; 95% CI, 1.4 to 29) (Fig. 1). The RR of IPD for HIV-infected patients was 24 (95% CI, 15 to 38), with an incidence of 414 per 100,000 (95% CI, 268 to 611) among HIV-infected patients versus 18 (95% CI, 13 to 24) among HIV-uninfected/status unknown cases and was highest among persons 18 to 54 years old (RR, 47; 95% CI, 25 to 89). The RRs for HIV infected versus HIV uninfected/status unknown, stratified by black and all other race/ethnicity groups, were 19 (95% CI, 11 to 33) and 31 (95% CI, 12 to 85), respectively.

Table 1 describes the demographic and clinical characteristics of the 72 collected cases. Of the adult cases, 25/63 (40%) were known to be HIV infected. There were no documented HIV-infected pediatric cases. The case fatality ratio was 19% (12/63) in adults and 11% (1/9) in children. Among HIV-infected adults for whom vaccination status was known, 13/21 (62%) had received the 23-valent pneumococcal polysaccharide vaccine (PPV23). Among children whose PCV7 status was known, 3/5 (60%) were up-to-date with PCV7.

As pneumococcal conjugate vaccine came into increasing use in Newark (2), VT IPD disappeared from the municipality (Fig. 2). Only one case of VT IPD, serotype 9V, occurred in an HIV-infected adult vaccinated with PPV23. Three cases of vaccine-related serotype 6A, for which substantial cross-protection has been demonstrated (20), also occurred in adults. The majority of NVT IPD was caused by serotypes 19A (28%), 19F (13%), and 14 (13%).

### Table 1. Demographic and clinical characteristics of Newark IPD cases by HIV status

| Demographic group or clinical characteristic | HIV infected (n = 25) | HIV uninfected or status unknown (n = 47) | Total cases (n = 72) |
|---------------------------------------------|----------------------|------------------------------------------|---------------------|
| Women, n (%)                                | 14 (56)              | 26 (55)                                  | 40 (56)             |
| Median age (yr)                              | 46                   | 53                                       | 52                  |
| Age group (yr), n (%)                        | 0 (0)                | 6 (13)                                   | 6 (8)               |
| 5–17                                        | 0 (0)                | 3 (6)                                    | 3 (4)               |
| 18–44                                       | 9 (36)               | 5 (11)                                   | 14 (19)             |
| 45–64                                       | 16 (64)              | 21 (45)                                  | 37 (51)             |
| ≥65                                         | 0 (0)                | 12 (26)                                  | 12 (17)             |
| Ethnicity, n (%)                             | 20 (80)              | 31 (66)                                  | 51 (71)             |
| Black not Hispanic                          | 5 (20)               | 12 (26)                                  | 17 (24)             |
| Hispanic                                    | 0 (0)                | 4 (8)                                    | 4 (5)               |
| Case fatality ratio, n (%)                   | 0 (0)                | 13 (28)                                  | 13 (18)             |
| Invasive pneumococcal disease, n (%)         | 1 (4)                | 4 (8)                                    | 5 (7)               |
| Meningitis                                  | 18 (72)              | 31 (66)                                  | 49 (68)             |
| Bacteremic pneumonia                        | 6 (24)               | 12 (26)                                  | 18 (25)             |
| Cerebrospinal fluid as source, n (%)         | 0 (0)                | 3 (6)                                    | 3 (4)               |
| Comorbid conditions, n (%)                   | 4 (16)               | 9 (19)                                   | 13 (18)             |
| Diabetes                                    | 6 (24)               | 9 (19)                                   | 15 (21)             |
| Renal disease                               | 4 (16)               | 8 (17)                                   | 12 (17)             |
| Chronic obstructive pulmonary disease        | 6 (24)               | 6 (13)                                   | 12 (17)             |

*The case fatality ratio is the proportion of cases in which the patient died prior to hospital discharge.*

Figure 1: Age distribution of invasive pneumococcal disease incidence (per 100,000) by race/ethnicity, Newark, NJ, December 2007 to November 2008. Age- and race-stratified incidences were calculated based on the 72 cases for which full data were available.

Figure 2: Pneumococcal serotype distribution in Newark, NJ, 2000 to 2005 and December 2007 to November 2008. Data are shown from an earlier, single-center study (18) conducted from 2000 to 2005 as well as the current prospective, multicenter analysis. Newark infant PCV7 coverage rates increased from 2002 to 2006: 2002 (31%), 2003 (58%), 2004 (71%), 2005 (76%), 2006 (80%), 2007 and 2008 not available (2). The gray area represents January 2006 to November 2007, a period when serotyping was not performed.
TABLE 2. Distribution of pneumococcal serotypes by HIV status

| Serotype | No. with serotype among: | HIV infected | HIV uninfected/ status unknown | Total |
|----------|--------------------------|--------------|-------------------------------|-------|
| PCV7<sup>a</sup> | 9V | 1 | 0 | 1 |
| &nbsp;&nbsp;&nbsp;&nbsp; | Subtotal | 1 | 0 | 1 |
| PCV10<sup>b</sup> | 1 | 0 | 1 | 1 |
| &nbsp;&nbsp;&nbsp;&nbsp; | 5 | 0 | 1 | 1 |
| &nbsp;&nbsp;&nbsp;&nbsp; | 7F | 0 | 1 | 1 |
| &nbsp;&nbsp;&nbsp;&nbsp; | Subtotal | 1 | 3 | 4 |
| PCV13<sup>c</sup> | 3 | 1 | 5 | 6 |
| &nbsp;&nbsp;&nbsp;&nbsp; | 6A | 1 | 2 | 3 |
| &nbsp;&nbsp;&nbsp;&nbsp; | 19A | 6 | 13 | 19 |
| &nbsp;&nbsp;&nbsp;&nbsp; | Subtotal | 9 | 23 | 32 |
| NVT | 22F | 4 | 4 | 8 |
| &nbsp;&nbsp;&nbsp;&nbsp; | 15A | 1 | 3 | 4 |
| &nbsp;&nbsp;&nbsp;&nbsp; | 11A | 2 | 1 | 3 |
| &nbsp;&nbsp;&nbsp;&nbsp; | 11B/C | 0 | 2 | 2 |
| &nbsp;&nbsp;&nbsp;&nbsp; | 20 | 1 | 1 | 2 |
| &nbsp;&nbsp;&nbsp;&nbsp; | 35B | 1 | 1 | 2 |
| &nbsp;&nbsp;&nbsp;&nbsp; | 8 | 0 | 2 | 2 |
| &nbsp;&nbsp;&nbsp;&nbsp; | Other | 5 | 7 | 12 |
| &nbsp;&nbsp;&nbsp;&nbsp; | Subtotal | 14 | 23 | 37 |
| Isolates with no extractable DNA | 2 | 1 | 3 |
| Total | 25 | 47 | 72 |

<sup>a</sup> PCV7 includes serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F.

<sup>b</sup> PCV10 includes the serotypes in PCV7 plus 1, 5, and 7F.

<sup>c</sup> PCV13 includes the serotypes in PCV10 plus 3, 6A, and 19A.

22F (12%), and 3 (8%) (Table 2). There were no statistically significant differences in the proportion of NVT or serotype 19A by HIV infected versus HIV uninfected/status unknown or black versus all others. The three CSF isolates were serotypes 11A, 12F, and nontypeable. Of note, 37/69 (54%) cases were black versus all others. The three CSF isolates were serotypes 19A by HIV infected versus HIV uninfected/status unknown or HIV uninfected/ status unknown/total.

A higher proportion of pediatric versus adult cases was caused by 19A (5/9 [56%] versus 14/60 [23%]; P = 0.06). A higher proportion of penicillin-nonsusceptible IPD cases (7/12 [58%]) was due to 19A than among penicillin-susceptible IPD cases (12/57 [21%]; P < 0.05). Serotype 19A occurred more frequently in the flu season (November to March) than in the non-flu season months (April to September; 14/38 [37%] versus 5/31 [16%]; P = 0.06).

IPD caused by VT serotypes has been nearly eliminated from the Newark population following the introduction of PCV7. These decreases occurred in conjunction with increasing PCV7 coverage rates among Newark children from 2002 to 2006. As reported for other populations (7–9, 14), by 2008 serotype 19A was the most common disease-causing pneumococcal serotype and accounted for the majority of the penicillin-nonsusceptible cases. If current serotype patterns persist, future vaccines targeting 19A would help to prevent a majority of IPD in our largely minority population with a high HIV prevalence.

Newark’s 1-year incidence of IPD in 2008 was 2.5 times higher than that described in the general U.S. population in 2006, likely due to the relatively high HIV prevalence, as well the high prevalence of other immunocompromising, chronic illnesses. In common with previous reports (5, 10, 15), we found a higher risk of IPD among black individuals compared to individuals of other races/ethnicities. The magnitude of the increased risk was most pronounced among persons ages 18 to 44 years old and exceeded the difference found in other studies (5).

Given our study design, we were unable to examine potential disparities in risk factors for IPD that may have contributed to the increased risk among black individuals. However, other authors have speculated that undocumented HIV infection and/or other immunomodulating conditions may contribute to the elevated relative risk (10). Potential miscategorization of HIV in the black population in our study was suggested by the lower racially stratified relative risk of IPD for HIV-infected cases compared with HIV-infected cases of all other races/ethnicities.

HIV-infected persons have historically had a 40-fold-higher risk of IPD than HIV-uninfected persons. In this population with a reported 2% HIV prevalence (11), IPD-HIV coinfection resulted in the highest burden of disease falling among young to middle-age adults, relative to young children and the elderly, a pattern of IPD very different from that in the general U.S. population (1). Roughly 40% of HIV-infected patients represented missed opportunities for vaccination with PPV23. Information was not available on CD4 count, antiretroviral therapy, or cotrimoxazole prophylaxis, limiting our ability to comment on the appropriate use of the full arsenal of preventive measures in this at-risk population.

Our study had several limitations. This multicenter study of all Newark IPD was conducted for only 1 year. A prior single-center study provided some insight into the serotype distribution during the early post-PCV7 years (18). However, we have not analyzed data on serotype distribution prior to PCV7 introduction. Therefore, we may not have a full understanding of the changes in individual nonvaccine serotypes since the introduction. Therefore, we may not have a full understanding of the changes in individual nonvaccine serotypes since the introduction of PCV7. Our case definition did not include sterile site pneumococcal isolates other than blood or CSF. Therefore, our estimates of incidence may be slight underestimates compared to those from national surveillance studies (1, 20).

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