

Epidemiologic Relation between HIV and Invasive Pneumococcal Disease in San Francisco County, California

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Background: Patients with AIDS have a high incidence of invasive pneumococcal disease, but no population-based data are available on secular trends or rates of this disease in specific demographic groups.

Objective: To compare clinical characteristics, rates, and trends of pneumococcal disease in HIV-infected and non-HIV-infected persons.

Design: Population-based laboratory surveillance and chart review.

Setting: All of the 13 microbiology laboratories in San Francisco County, California.

Patients: Persons who had a sterile site culture that was positive for *Streptococcus pneumoniae* between October 1994 and June 1997.

Measurements: Stratified incidence rates and adjusted rate ratios, serotyping of isolates, and comparison of secular trends and rates according to census tract by Poisson regression.

Results: Persons infected with HIV accounted for 54.2% of 399 patients 18 to 64 years of age who had pneumococcal disease. The incidence of pneumococcal disease per 100 000 person-years was 35.0 cases overall and 802.9 cases in patients with AIDS. Compared with persons who were not known to be HIV-infected, the rate ratio for patients with AIDS was 46.0 (95% CI, 36.0 to 58.9); 55.2% of cases were attributable to HIV. In HIV-infected patients, 82.5% of isolates were serotypes that are included in the pneumococcal polysaccharide vaccine. The incidence of pneumococcal disease in black patients with AIDS (2384.6 cases per 100 000 person-years) was 5.4 times that in nonblack patients with AIDS. Rates by census tract were inversely associated with income ($P < 0.001$). During the study period, the incidence of pneumococcal disease decreased from 10.6 cases per 1000 person-years to 4.2 cases per 1000 person-years in patients with AIDS ($P = 0.004$, Poisson regression).

Conclusions: In a community with a high prevalence of HIV infection, much of the burden of pneumococcal disease was attributable to AIDS. High incidence rates were seen in young adults and especially in black persons. Efforts to increase pneumococcal vaccination rates should target HIV-infected adults, particularly those living in poor urban areas.

Streptococcus pneumoniae is the leading cause of community-acquired bacterial pneumonia and bacteremia in HIV-infected persons (1–3). Persons infected with HIV currently account for at least 40% of all adult cases of invasive pneumococcal disease in many U.S. medical centers (4, 5). Pneumococcal disease can occur early in the course of HIV infection, before onset of other opportunistic infections specifically associated with AIDS (6–8), and recurrent infection is common (2, 8). Extremely high overall rates of invasive disease have been documented in persons with AIDS (6, 8, 9), but no detailed data are available on disease rates in different demographic groups.

Recent reports have shown substantial decreases in the incidence of AIDS-related opportunistic illnesses (10). However, no population-based data are available on secular trends of incidence of pneumococcal disease in patients with AIDS. To help focus preventive efforts, we evaluated the epidemiologic and clinical effects of the AIDS epidemic on invasive pneumococcal disease by conducting population-based surveillance in San Francisco County, California, a large metropolitan area with the fourth-highest incidence of AIDS in the United States (11).

Methods

Population-Based Surveillance

Cases of invasive pneumococcal disease in residents of San Francisco County, California (1996 population, 735 315 persons), were identified prospectively through active, laboratory-based surveillance. Project personnel contacted all of the 13 clinical microbiology laboratories in the county bi-weekly. They reviewed medical records by using a standard case report form to obtain demographic information, limited clinical information (including clinician's diagnoses of the syndromes associated with invasive pneumococcal disease), and HIV antibody status. Data on ethnicity were collected by chart review and were classified according to the standard Centers for Disease Control and Prevention (CDC) categories: white, black, American Indian–Alaskan Native, Asian–Pacific Islander, not specified, or unknown. Ethnic origin was classified as Hispanic, non-Hispanic, or unknown. *Streptococcus*

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pneumoniae isolates were identified by standard methods and were serotyped at the CDC with the Quellung reaction (12). All laboratories were audited at least bimonthly to ensure completeness of reporting. Active surveillance for invasive pneumococcal disease, as part of the California Emerging Infections Program, was approved by the California Committee for the Protection of Human Subjects and by the institutional review board of the University of California at Berkeley, Berkeley, California.

Case Definitions

A case of invasive pneumococcal disease was defined as isolation of *S. pneumoniae* from a normally sterile site (such as blood or cerebrospinal fluid) between October 1994 and June 1997 in a resident of the surveillance area. Recurrent disease was defined as isolation of *S. pneumoniae* from a normally sterile site more than 7 days after the original episode. Case-fatality ratio refers to the proportion of cases that were fatal during the study period. Cases of AIDS were defined according to the CDC revised case definition (13).

Calculation of Incidence Rates

Demographic and clinical data were analyzed for cases of pneumococcal disease that occurred between October 1994 and December 1996, before a major decrease in incidence occurred. To control for seasonal variability, incidence rates were calculated from cases that occurred between January 1995 and December 1996 by using the U.S. Bureau of Census population estimates. To calculate the incidence of invasive pneumococcal disease in persons with AIDS, we used as a denominator the number of persons living with AIDS during each

month of the study that was reported to the San Francisco Department of Public Health's AIDS Office by 1 April 1998. For this surveillance system, the completeness of reporting is 97%, with a median reporting delay of 1 month (14). The average monthly incidence of invasive pneumococcal disease was calculated by dividing the total number of pneumococcal cases in persons with AIDS by the sum of the number of patients with AIDS who were alive during each month; this average monthly incidence was multiplied by 12 to estimate the annual incidence (6). On average, 7295 persons with AIDS 18 to 64 years of age were living in San Francisco during the study period.

To evaluate secular trends, rates of pneumococcal disease in patients with AIDS and in those without known HIV infection were calculated twice: for each 3-month period from October 1994 through June 1997 and for three consecutive periods of peak respiratory infection (October to March). Because HIV infection is not reported in California, exact denominator information was not available for persons who were HIV-positive but did not have AIDS. These persons were excluded from the analyses of trend.

Statistical Analysis

Data were analyzed by using SAS, version 6.12 (SAS Institute, Inc., Cary, North Carolina), and Epi-Info software, version 6.04 (CDC, Atlanta, Georgia). Proportions were compared by using the chi-square test, and continuous variables were compared by using the Kruskal-Wallis test. For the first event of pneumococcal disease, rate ratios and 95% CIs—adjusted for age (in 10-year age groups), ethnicity (black persons compared with nonblack persons)

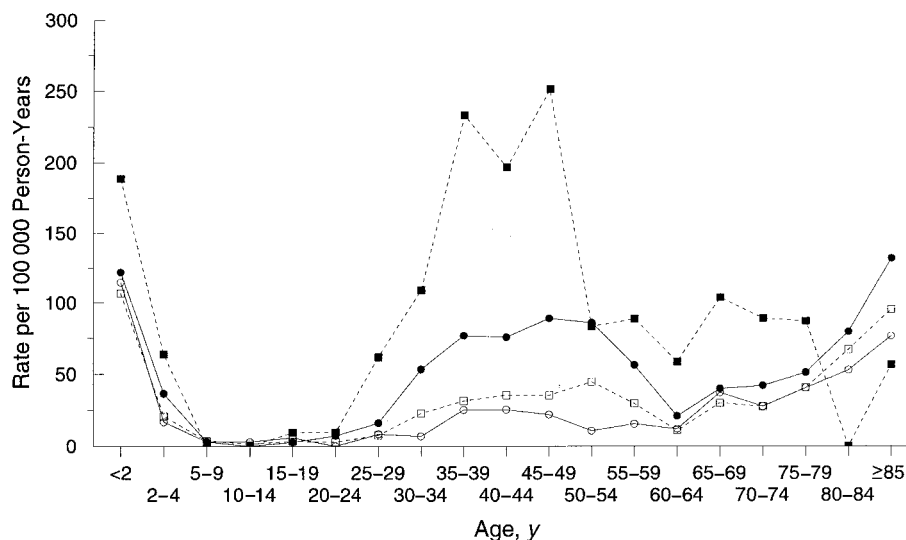


Figure 1. Incidence of invasive pneumococcal disease by age, sex, and ethnicity (San Francisco, California, 1995-1996). Black squares represent incidence among black persons, white squares represent incidence among nonblack persons, black circles represent incidence among men, and white circles represent incidence among women.

sons) and sex (where appropriate)—were calculated by using Poisson regression (15). To identify predictors of death and of recurrence of pneumococcal illness in a multivariable analysis, we used Poisson regression models and the SAS GENMOD procedure (16). In this analysis, death and recurrent infection were the outcome variables and were adjusted for sex; ethnicity; age; and other potential confounders, including HIV status, injection drug use, alcohol misuse, chronic illness, and immunocompromising illnesses other than HIV infection. We also used a Poisson regression model to evaluate whether the observed changes in the incidence of pneumococcal disease in persons with AIDS were statistically significant. In addition to the individual-level analyses, we performed ecological analyses to determine the association between census population variables (median household income and proportion of black persons) and disease incidence according to census tract by using a Poisson model that tested for effects of both ethnicity and income.

Results

All Age Groups

Between October 1994 and December 1996, 602 cases of invasive pneumococcal disease were identified. The overall incidence was 34.0 cases per 100 000 person-years. Patients ranged in age from 2

months to 98 years (median, 45 years); 69.3% of patients were male. Overall, 70 patients (12.6%) died. Case-fatality ratios were similar according to sex and ethnicity. Information on the outcome of illness was missing for 45 cases (7.5%). For persons who were at least 65 years of age, 23.4% of cases were fatal. The incidence per 100 000 person-years was highest in children younger than 2 years of age (118.2 cases) and in persons at least 65 years of age (48.3 cases). The age-adjusted rates per 100 000 person-years were 47.7 cases for male patients, 20.3 cases for female patients, 96.0 cases for black persons, and 23.5 cases for nonblack persons (**Figure 1**). Because 99.3% of HIV-infected patients were 18 to 64 years of age, we restricted all subsequent analyses to those in this age group.

Demographic and Clinical Characteristics of Patients 18 to 64 Years of Age

Persons 18 to 64 years of age accounted for 399 (66.3%) of all cases of invasive pneumococcal disease. Information on HIV status was available for 380 of these patients (95.2%). For 206 patients (54.2%), HIV infection was documented in medical records; 136 patients (35.8%) had AIDS, and 70 (18.4%) were HIV-positive but did not have AIDS when pneumococcal disease was diagnosed (**Table 1**). Overall, 54.5% of patients were white and 37.9% were black. The ratio of men to women was 7:1 in

Table 1. Characteristics of 380 Patients 18 to 64 Years of Age with Invasive Pneumococcal Disease, according to HIV Infection Status (San Francisco County, California, 1994–1996)*

Characteristic	Patients with AIDS (n = 136)	HIV-Positive Patients (n = 70)	Patients without Known HIV Infection (n = 174)	All Patients (n = 380)
Sex, n (%)†				
Male‡	119 (87.5)	57 (81.4)	128 (73.6)	304 (80.0)
Female	17 (12.5)	13 (18.6)	45 (25.9)	75 (19.7)
Ethnicity, n (%)				
White	77 (56.6)	41 (58.6)	89 (51.2)	207 (54.5)
Black	55 (40.4)	22 (31.4)	67 (38.5)	144 (37.9)
Asian–Pacific Islander	0 (0)	0 (0)	11 (6.3)	11 (2.9)
American Indian–Alaskan Native	0 (0)	0 (0)	2 (1.1)	2 (0.5)
Not specified	1 (0.7)	0 (0)	0 (0)	1 (0.3)
Unknown	3 (2.2)	7 (10)	5 (2.9)	15 (3.9)
Ethnic origin, n (%)				
Hispanic	12 (8.8)	10 (14.3)	23 (13.2)	45 (11.8)
Non-Hispanic	119 (87.5)	53 (75.7)	146 (83.9)	318 (83.7)
Unknown	5 (3.7)	7 (10)	5 (2.9)	17 (4.5)
Median age, y	38.5	40.0	44.0	41.0
Recurrent illness, n (%)	20 (14.7)	9 (12.9)	5 (2.9)	34 (8.9)
Case-fatality ratio	16 (11.8)	3 (4.3)	15 (8.6)	34 (8.9)
Predisposing conditions, n (%)§				
Chronic illness	5 (3.7)	6 (8.6)	34 (19.5)	45 (11.8)
Immunocompromising condition other than HIV infection¶	14 (10.3)	4 (5.7)	29 (16.7)	47 (12.4)
Alcohol misuse	27 (19.9)	16 (22.9)	71 (40.8)	114 (30.0)
Injection drug use	57 (41.9)	26 (37.1)	23 (13.2)	106 (27.9)

* No data on HIV status were available for 19 (4.8%) of 399 patients.

† Information on sex was unknown for 1 patient.

‡ Patients who had AIDS compared with patients who did not have confirmed HIV infection. Relative risk, 1.2 (95% CI, 1.1–1.3).

§ Patients may have >1 predisposing condition.

|| Presence of at least 1 of the following conditions: chronic cardiopulmonary disease (chronic heart failure, chronic obstructive pulmonary disease), cirrhosis, diabetes mellitus, or chronic renal disease (data obtained from reference 17).

¶ Leukemia, lymphoma, Hodgkin disease, multiple myeloma, generalized malignant condition, nephrotic syndrome, immunosuppressive chemotherapy or organ or bone marrow transplantation.

Table 2. Incidence of Invasive Pneumococcal Disease among Black Patients and Nonblack Patients 18 to 64 Years of Age, according to Sex and AIDS Status (San Francisco County, California, 1995–1996)*

Characteristic	All Patients		Black Patients		Nonblack Patients†	
	Cases	Rate per 100 000 Person-Years	Cases	Rate per 100 000 Person-Years	Cases	Rate per 100 000 Person-Years
	<i>n</i>		<i>n</i>		<i>n</i>	
Overall	343	35.0	124	127.9	204	23.1
Sex						
Male	275	54.6	93	193.0	170	37.3
Female	67	14.1	31	63.5	34	8.0
AIDS status‡						
AIDS	117	802.9	47	2384.6	67	531.7
No known HIV infection	149	15.7	56	60.2	88	10.2

* No data on ethnicity were available for 15 patients; sex was unknown for 1 patient. Because no appreciable differences were observed in rates between non-Hispanic white persons and Hispanic white persons, these groups were combined for analysis. Patients of unknown ethnicity were excluded.

† Includes Asian–Pacific Islanders and American Indian–Alaskan Natives.

‡ Data on AIDS status were missing for 17 patients; 60 HIV-positive persons who did not have AIDS were excluded.

persons with AIDS, 4.4:1 in persons with HIV infection, and 2.8:1 in persons without documented HIV infection. Persons infected with HIV were younger than those without known HIV infection ($P = 0.009$ for the comparison of mean ages), and persons who had AIDS were more likely to be men (Table 1). Patients with AIDS accounted for 38.2% of cases of pneumococcal infection in black persons and 37.2% of cases in white persons. Black patients and white patients with AIDS had similar mean ages (40.6 years and 39.3 years, respectively). The most common clinical syndromes associated with invasive pneumococcal disease were bacteremic pneumonia (83.9% of cases), bacteremia without focus (10.8% of cases), and meningitis (3.2% of cases). The frequencies of these syndromes did not differ significantly between HIV-infected patients and those who were not known to have HIV infection.

Incidence of Invasive Pneumococcal Disease by AIDS Status, Ethnicity, and Sex

The overall incidence of invasive pneumococcal disease for persons 18 to 64 years of age was 35.0 cases per 100 000 person-years (Table 2). The overall crude rate ratio for comparing men with women was 3.9; the age-adjusted and ethnicity-adjusted rate ratio was also 3.9 (95% CI, 2.9 to 5.2 [54.6 cases per 100 000 person-years compared with 14.1 cases per 100 000 person-years]). Compared with women of the same ethnic background, the rate ratios for black men and nonblack men were 3.0 (CI, 2.0 to 4.6) and 4.7 (CI, 3.2 to 6.8), respectively. When we compared black patients with nonblack patients, the crude rate ratio for developing pneumococcal disease was 5.5 and the age-adjusted and sex-adjusted rate ratio was 5.4 (CI, 4.3 to 6.8), regardless of AIDS status.

Compared with persons who were not known to have HIV infection, the crude rate ratio for developing invasive pneumococcal disease in persons

with AIDS was 51.3 (CI, 40.3 to 65.3 [802.9 cases per 100 000 person-years compared with 15.7 cases per 100 000 person-years]). The age-adjusted and ethnicity-adjusted rate ratio was 46.0 (CI, 36.0 to 58.9). Because our study included only a few women with AIDS, the rate ratio in persons with AIDS compared with that in persons who did not have documented HIV infection was not adjusted for sex. In patients with AIDS, the woman-to-man rate ratio was 2.8 (CI, 1.6 to 4.8 [2040.8 cases per 100 000 person-years compared with 729.3 cases per 100 000 person-years]). However, our analysis included only 15 women with AIDS. Black patients with AIDS had the highest observed rate of pneumococcal infection (2384.6 cases per 100 000 person-years). In patients with AIDS, the rate ratio for comparing black patients with nonblack patients was 4.5 (CI, 3.1 to 6.5). In persons 18 to 64 years of age, 55.2% of all cases of pneumococcal disease were attributable to HIV infection (population attributable risk percentage).

Mortality Rate and Recurrent Infection

Thirty-four nonelderly adults (8.9%) died. Case-fatality ratios were similar according to ethnicity and sex regardless of HIV status. In multivariable analysis, the adjusted rate ratios for death were 1.8 (CI, 0.7 to 4.4) for patients with AIDS and 0.7 (CI, 0.2 to 2.0) for HIV-positive patients compared with patients who were not known to be HIV-infected. Alcohol misuse was the only factor independently associated with death (adjusted rate ratio, 2.8 [CI, 1.4 to 6.0]). By December 1996, 32 episodes of recurrent disease had occurred among the 346 patients who survived their first episode. In multivariable analysis, HIV-infected persons were almost 5 times more likely than persons without documented HIV infection to develop recurrent pneumococcal disease (Table 3). In addition, injection drug use and immunocompromising illnesses other than HIV

infection were independently associated with recurrent disease.

Capsular Serotypes

In patients for whom data on HIV status were available, 295 isolates (77.6%) were available for serotyping. The 23-valent polysaccharide vaccine serotypes accounted for 82.5% of isolates in HIV-infected patients and 83.0% of isolates in non-HIV-infected patients (Table 4). However, only 43.8% of the isolates in HIV-infected patients were serotypes represented in the candidate 7-valent conjugate vaccine. The proportions of vaccine-related and non-vaccine-related serotypes did not differ significantly by HIV status or ethnicity.

Secular Trends

Figure 2 shows the trends in incidence of pneumococcal disease in persons with AIDS and in those without known HIV infection. Patients who were HIV-positive were excluded because accurate denominator information was not available. The quarterly incidence of pneumococcal disease in patients with AIDS decreased from 10.6 cases per 1000 person-years to 4.2 cases per 1000 person-years from October 1994 through June 1997; this decrease was found to be significant by Poisson regression ($P = 0.004$). The most substantial decrease occurred from 1996 to 1997 (Figure 2). These changes were distinct from seasonal variations: During three consecutive periods of peak respiratory infection from October 1994 through March 1997, the incidence of invasive pneumococcal disease per 1000 person-years in persons with AIDS decreased by 49.5%, from 11.2 cases to 9.1 cases to 5.6 cases ($P = 0.01$). In contrast, the incidence of pneumococcal disease in persons not known to have HIV infection showed only the expected seasonal variation from October 1994 through June 1997, and no trend was observed ($P > 0.2$). During the three consecutive respiratory

infection seasons, the rates per 1000 person-years in persons without known HIV infection first increased from 0.20 cases to 0.24 cases and then decreased to 0.17 cases.

Ecological Analysis

We analyzed the incidence rates for cases of pneumococcal disease in persons 18 to 64 years of age by median household income of the residence census tract and by ethnicity. In black persons, the incidence per 100 000 person-years decreased almost linearly from 113.0 cases in census tracts with incomes less than \$15 000 to 34.2 cases in tracts with incomes more than \$45 000. For nonblack persons, the rates per 100 000 person-years decreased similarly, from 61.6 cases to 15.8 cases. When we tested for effects of both ethnicity and income in a Poisson model, both median household income ($P < 0.001$) and black ethnicity ($P < 0.001$) were highly significant in determining the incidence rate of pneumococcal disease. The highest rates of disease occurred in a few inner-city census tracts with median household incomes less than \$20 000. Homeless persons, who accounted for 14% of cases, were excluded from the census tract analysis.

Discussion

Incidence rates of invasive pneumococcal disease are usually high in young children and elderly persons but low in young and middle-aged adults. Our findings highlight a changing epidemiologic pattern in a community with a high prevalence of HIV infection, which leads to high rates of pneumococcal disease in young adults. The overall incidence of invasive pneumococcal disease in San Francisco County is the highest reported in the continental United States (18, 19). We found that in persons with AIDS, the risk for invasive pneumococcal dis-

Table 3. Recurrent Pneumococcal Illness among Patients 18 to 64 Years of Age (San Francisco County, California, 1994–1996)

Characteristic	Patients (n = 346)	Patients with Recurrent Illness*	Crude Rate Ratio (95% CI)	Adjusted Rate Ratio (95% CI)†
	n	n (%)		
HIV status				
AIDS	120	19 (15.8)	6.3 (2.2–18.0)	4.7 (1.6–17.0)
HIV-positive	67	9 (13.4)	5.3 (1.7–16.7)	4.8 (1.4–18.5)
No known HIV infection	159	4 (2.5)	Referent	Referent
Injection drug use	92	17 (18.5)	3.2 (1.6–6.1)	2.3 (1.0–5.3)
Alcohol misuse	96	8 (8.3)	0.9 (0.4–1.9)	1.2 (0.5–2.7)
Chronic illness	45	3 (6.7)	0.7 (0.2–3.1)	1.0 (0.2–3.1)
Immunocompromising condition other than HIV infection‡	40	6 (15.0)	1.8 (0.8–4.0)	3.4 (1.2–8.6)

* Defined as those who survived a first episode of pneumococcal disease. Data on outcome of the first episode were missing for 27 patients. Relative risks were calculated by using cases with known outcomes through December 1996.

† Calculated by using a Poisson regression model with recurrent illness as the outcome variable, with adjustment for age, ethnicity, sex, and all of the other listed variables.

‡ Leukemia, lymphoma, Hodgkin disease, multiple myeloma, generalized malignant condition, nephrotic syndrome, immunosuppressive chemotherapy, or organ or bone marrow transplantation.

ease was 46 times higher than that in persons without known HIV infection; 55.2% of the disease burden among adults 18 to 64 years of age and one third of all pneumococcal disease could be attributed to HIV infection. Black patients with AIDS had an extremely high incidence of pneumococcal disease. Our data also indicate that invasive disease due to *S. pneumoniae* decreased dramatically from 1994 to 1997 in persons with AIDS.

Several community-based studies have found that black persons have a threefold to fivefold higher rate of invasive pneumococcal disease than white persons (9, 18, 19). We found higher rates in black adults than in nonblack adults, regardless of AIDS status. It is not known why black patients with AIDS have a greater risk for pneumococcal disease than nonblack patients with AIDS. However, this trend may reflect socioeconomic factors or overrepresentation of blacks among persons with limited access to health care, which results in delayed diagnosis of HIV infection and less frequent use of pneumococcal vaccine, chemoprophylaxis against opportunistic infections, and potent antiretroviral therapy (20). A recent national survey also suggested that black persons, women, uninsured persons, and Medicaid-insured persons received less optimal patterns of care for HIV infection (21).

In an ecological analysis, we found a strong inverse relation between incidence of pneumococcal disease and the median household income of the census tract in which patients resided; this supports the notion that some of the rate differential between black persons and nonblack persons may be explained by socioeconomic factors (22). In addition, cases in adults were geographically clustered in a few inner-city, low-income census tracts. This association is unlikely to be confounded by AIDS because the census tracts with the highest incidence of pneumococcal disease differed from those with the highest reported prevalence of AIDS (23). However, the association between the incidence of pneumococcal disease and the median household income of census tracts is vulnerable to ecological bias because the aggregate-level (census tract) characteristics may not necessarily represent individual-level patient characteristics. The HIV epidemic disproportionately affects persons in ethnic minority groups (10, 11), and pneumococcal disease still seems to be a disease of poverty. These inequalities in health highlight the need for targeted preventive efforts, especially among black HIV-infected patients living in poor urban areas.

In an earlier study conducted at 10 San Francisco hospitals from 1983 to 1987, HIV-infected persons accounted for 26% of adult cases of pneumococcal bacteremia, and the rate in patients with AIDS was estimated to be as high as 1% per year (6). Our

Table 4. Serotypes of *Streptococcus pneumoniae* Isolates among 295 Patients 18 to 64 Years of Age with Invasive Pneumococcal Disease, according to HIV Status (San Francisco County, California)

Serotype	Isolates			
	All Patients	Patients with AIDS	HIV-Positive Patients	Patients without Known HIV Infection
	← n (%) →			
4	43 (14.6)	14 (13.6)	10 (17.5)	19 (14.1)
6A	8 (2.7)	4 (3.9)	1 (1.8)	3 (2.2)
6B	10 (3.4)	4 (3.9)	3 (5.3)	3 (2.2)
9N	23 (7.8)	9 (8.7)	5 (8.8)	9 (6.7)
9V	19 (6.4)	5 (4.9)	4 (7.0)	10 (7.4)
14	28 (9.5)	10 (9.7)	3 (5.3)	15 (11.1)
18C	4 (1.4)	1 (1.0)	2 (3.5)	1 (0.7)
19A	10 (3.4)	6 (5.8)	1 (1.8)	3 (2.2)
19F	7 (2.4)	4 (3.9)	0 (0)	3 (2.2)
23F	13 (4.4)	8 (7.8)	2 (3.5)	3 (2.2)
Other	130 (44.1)	38 (36.8)	26 (45.5)	66 (49.0)
Total	295 (100)	103 (100)	57 (100)	135 (100)
Conjugate vaccine types*	124 (42.0)	46 (44.7)	24 (42.1)	54 (40.0)
23-valent polysaccharide vaccine type†	244 (82.7)	86 (83.5)	46 (80.7)	112 (83.0)

* 4, 6B, 9V, 14, 18C, 19F, and 23F.

† Includes all serotypes in the 23-valent pneumococcal polysaccharide vaccine.

data indicate that HIV now accounts for 54% of cases, but the incidence in patients with AIDS seems to be decreasing. Excluding HIV-positive patients from the secular trend analysis would not affect the trend in patients with AIDS because the exact numerator and denominator were known for this group. In patients with pneumococcal disease, the absolute numbers of HIV-infected persons without AIDS did not increase during the study. If the unknown proportion of HIV-infected persons without AIDS increased over time in the population denominator for quarterly rates, it could theoretically show a decreasing trend in incidence of invasive pneumococcal disease in persons without known HIV infection. However, the proportion would be negligible compared with the total population denominator, and such a trend was not observed in this group.

Coinciding with our study period, from 1994 to 1997, incidence of certain AIDS-related opportunistic infections and of deaths from these infections decreased markedly (10). These reductions in deaths and disease have been attributed to the effect of potent antiretroviral therapy (24). However, no data are available on the specific effect of such therapy on risk for pneumococcal disease in HIV-infected persons.

Although our study did not include information on the use of antiretroviral therapy or routine chemoprophylaxis against opportunistic infections, the HIV treatment practices in San Francisco County are probably comparable to those in other urban areas in the United States. In San Francisco

County, use of potent antiretroviral therapy was uncommon until the end of 1995 and then increased rapidly in 1996 and 1997 (25). The observed 49.5% decrease in the incidence of pneumococcal disease in patients with AIDS may therefore be associated with wider use of highly active antiretroviral therapy, including protease inhibitors.

Because the burden of pneumococcal disease in San Francisco County was strongly associated with HIV infection, the decrease in HIV-attributable risk for pneumococcal disease may have a major effect on public health in communities with a high prevalence of HIV. Previous analysis suggested that pneumococcal surveillance may be a sensitive epidemiologic indicator of increases in the immunosuppressed HIV-infected population (9). Our data suggest that pneumococcal surveillance may also reflect decreases in rates of HIV due to response to therapy or use of preventive services.

We may have underestimated the number of persons with pneumococcal disease who were included in the HIV-infected category because we included only patients who had documentation of HIV in their medical records. Many patients were probably not tested for HIV, and some who had known risk factors for HIV infection (such as injection drug use) did not have documentation of HIV serostatus and may have been misclassified as noninfected. This may be reflected in our baseline rate of pneumococcal disease in adults without known HIV infection, which is somewhat higher than that reported in other areas in the United States (9, 26) and that reported before the AIDS epidemic (18, 19). Be-

cause patients with AIDS are less likely to be misclassified and because AIDS reporting was almost complete (14), the rates for persons with AIDS are probably accurate.

One limitation of our study is that accurate data were not available on CD4 cell counts and pneumococcal vaccination status of HIV-infected patients. However, a CDC study on the efficacy of pneumococcal vaccine, which was conducted in San Francisco from 1992 to 1995, found that only 33.5% of 486 HIV-infected persons had been vaccinated (CDC. Unpublished data). In that study, determination of vaccination status was particularly thorough and included contact with the primary care providers of all patients. Another study found that only 37% of 9737 HIV-infected persons in more than 90 clinics in 9 U.S. cities had received pneumococcal vaccine between January 1990 and September 1992 (27). However, use of vaccination varied substantially among cities and individual clinics.

The distribution of pneumococcal serotypes that caused illness was similar for HIV-infected patients and non-HIV-infected patients (5, 6); 83% of the isolates were serotypes that are included in the current 23-valent polysaccharide vaccine. However, serotypes included in a 7-valent pneumococcal conjugate vaccine that will probably be licensed in the United States in the near future accounted for only 44% of the isolates. Because of the limited number of serotypes in the conjugate vaccine and the broad distribution of serotypes in infected adults, use of the conjugate vaccine alone will not prevent invasive pneumococcal disease in HIV-infected persons.

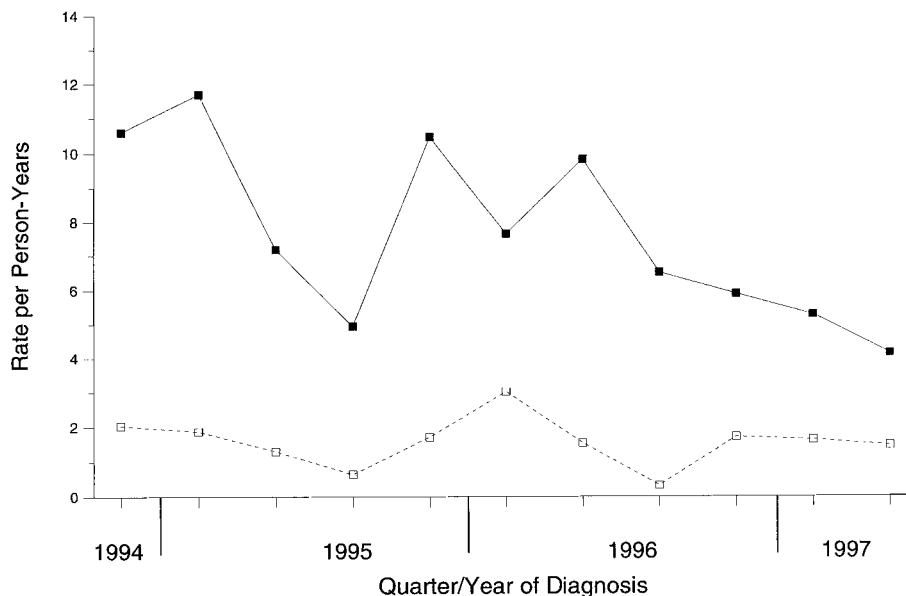


Figure 2. Incidence of invasive pneumococcal disease among persons with AIDS and those without known HIV infection by quarter/year of diagnosis (San Francisco, California, October 1994 through June 1997). Black squares represent incidence among persons with AIDS, and white squares represent incidence among persons without known HIV infection. Points represent quarterly incidence. Rates for persons with AIDS are shown per 1000 person-years. For persons without known HIV infection, rates are shown per 10 000 person-years.

However, it may be possible to prime the immune system in adults by administering the 7-valent conjugate vaccine. A subsequent dose of 23-valent polysaccharide vaccine could then be given to induce a booster response to the serotypes present in both vaccines and the primary T-cell independent responses to the 16 serotypes that are included only in the polysaccharide vaccine (28). Additional data are needed to determine the immunogenicity, safety, and effectiveness of this approach in HIV-infected persons.

The precise deficits in the immune system that predispose HIV-infected persons to pneumococcal infections are not well characterized, but progressive loss of the ability to produce specific functional antibodies is probably a contributing factor (4). However, some asymptomatic HIV-infected persons respond well to pneumococcal polysaccharide vaccine, and the immunologic response seems to be best in the early stages of HIV infection (29, 30). Because zidovudine therapy has been shown to improve immune responses to pneumococcal polysaccharide vaccine in patients with AIDS (31), the effect of potent antiretroviral therapy on antibody responses to pneumococcal vaccine warrants further study. In one case-control study, zidovudine therapy and pneumococcal vaccination in HIV-infected persons with CD4 counts greater than 200 cells/mm³ were associated with a lower risk for pneumococcal infection (32). Although limited data are available on the effectiveness of pneumococcal polysaccharide vaccine in HIV-infected persons, the high rate of disease and the apparent safety and potential benefits of the vaccine justify its use (33).

Our findings strongly confirm several treatment and prevention implications that are useful for clinicians who care for HIV-infected persons and clinicians who practice in communities that have a high prevalence of HIV infection. Persons infected with HIV are at increased risk for invasive pneumococcal disease and are predisposed to recurrences; however, they do not have an increased mortality rate due to pneumococcal disease. If pneumococcal bacteremia is diagnosed in an adult younger than 65 years of age who has no other risk factors for pneumococcal disease, HIV testing is indicated. Early diagnosis is important because a clear benefit can be derived from potent antiretroviral therapy. In addition, HIV-infected persons should be vaccinated as soon as possible after a confirmed diagnosis to increase the opportunity for a functional immune response (17, 34). Most efforts to increase rates of pneumococcal vaccination have targeted elderly persons, but many HIV-infected, nonelderly adults who have access to medical care may not be vaccinated (27). Therefore, efforts to increase pneumococcal

vaccination should also target HIV-infected adults, particularly those living in poor urban areas.

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