Pneumococcal Disease among Human Immunodeficiency Virus–Infected Persons: Incidence, Risk Factors, and Impact of Vaccination

Mark S. Dworkin,[1,a] John W. Ward,[1,3] Debra L. Hanson,[1] Jeffrey L. Jones,[1,2] Jonathan E. Kaplan,[1,2] and the Adult and Adolescent Spectrum of HIV Disease Project[b]

[1]Division of HIV/AIDS Prevention–Surveillance and Epidemiology, National Center for HIV, STD, and TB Prevention, [2]National Center for Infectious Diseases, and [3]Epidemiology Program Office, Centers for Disease Control and Prevention, Atlanta

To determine the factors associated with pneumococcal disease (pneumococcal pneumonia or invasive disease) and the impact of pneumococcal vaccine in HIV-infected persons, we analyzed patient data collected by the Adult and Adolescent Spectrum of HIV Disease Project for person-time between January 1990 and December 1998. Among 39,086 persons with 71,116 person-years (py) of observation, 585 episodes of pneumococcal disease were diagnosed (incidence, 8.2 episodes per 1000 py). Factors associated with an increased risk for pneumococcal disease ($P < .05$) included injection drug use (adjusted relative risk [RR], 1.5) and blood transfusion (RR, 2.0) as the mode of HIV transmission (referent, male-male sex); black race/ethnicity (RR, 1.5; referent, white race); history of acquired immunodeficiency syndrome (AIDS)–defining opportunistic illness (RR, 2.1); a $CD4^+$ cell count of 200–499 cells/μL (RR, 2.5) or <200 cells/μL (RR, 3.7; referent, $CD4^+$ cell count of $\geq$500 cells/μL); and alcoholism (RR, 2.0). Factors associated with a decreased risk included prescription of antiretroviral therapy (RR for monotherapy, 0.6; for dual therapy, 0.7; for triple therapy, 0.5) and pneumococcal vaccination (RR for persons vaccinated at a $CD4^+$ cell count of $\geq$500 cells/μL, 0.5). We recommend that pneumococcal vaccine be given to HIV-infected persons before profound immunosuppression has occurred.

Infection with *Streptococcus pneumoniae* is the most common cause of bacterial pneumonia among HIV-infected persons in the United States [1]. It has been estimated to occur 100 times more frequently among such persons than among the general population [2]. Recurrence is relatively common (13% of cases recur within 6 months), and the reported mortality rate among HIV-infected persons with bacteremic pneumococcal pneumonia is 5%–11% [3].

Immunization with a single dose of 23-valent polysaccharide pneumococcal vaccine is recommended for HIV-infected adolescents and adults who have a $CD4^+$ T lymphocyte count of $\geq$200 cells/μL; it is optional for persons who have a $CD4^+$ cell count of <200 cells/μL [4]. These recommendations were based on the results of 2 studies that predated the use of highly active antiretroviral therapy and virus load monitoring [5, 6]. Clinical trial data that demonstrate the efficacy of pneumococcal vaccine among HIV-infected persons are scarce. To describe the incidence and risk factors of

Received 12 May 2000; revised 14 July 2000; electronically published 28 February 2001.

[a] Present affiliation: Illinois Department of Public Health, Chicago.

[b] Investigators are listed in the Appendix.

Reprints: National Center for HIV, STD, and TB Prevention, Office of Communications, Centers for Disease Control and Prevention, Mail Stop E-06, Atlanta, GA 30333. Correspondence: Dr. Mark S. Dworkin, State Epidemiologist, Illinois Department of Public Health, 160 N. LaSalle St., #7 South, Chicago, IL 60601 (mdworkin@idph.state.il.us).

Clinical Infectious Diseases 2001; 32:794–800

1058-4838/2001/3204-0016$03.00

pneumococcal disease and the impact of pneumococcal vaccine, we analyzed data collected throughout the 1990s by the Adult and Adolescent Spectrum of HIV Disease Project (ASD), a large, diverse cohort of HIV-infected persons in the United States. Our results reinforce the importance of administration of pneumococcal vaccine to HIV-infected persons early during the course of the infection.

METHODS

The methods used by the ASD, a national surveillance project of the Centers for Disease Control and Prevention in collaboration with 11 state and local health departments, have been reported elsewhere [7, 8]. The staff of the ASD abstracts data from the medical records of HIV-infected patients at selected health care facilities. Initial abstraction of data from these records involves collection of information on demographics, the mode of exposure to HIV, previous occurrences of conditions listed in the surveillance case definition of AIDS [9] and of other conditions, types of medications prescribed, and $CD4^+$ cell counts recorded during the year before patient selection. The initial data abstraction is followed by abstractions that are performed every 6 months until the patient either dies or is lost to follow-up. ASD staff members began abstracting data from medical records at project sites in 1990 (Atlanta, Dallas, Houston, San Antonio, Denver, Detroit, Los Angeles, New Orleans, and Seattle), 1991 (New York City), and 1992 (Bayamon, Puerto Rico). Participating facilities include hospitals, outpatient offices, and emergency departments.

Data were collected through April 1999 and reflect follow-up observations that occurred from January 1990 through December 1998. The cumulative duration of follow-up for the population was used to calculate person-time (expressed as "person-years" [py] of follow-up). The data set was restricted to 6-month follow-up intervals, during which time either a health care visit occurred (e.g., for an outpatient visit, hospitalization, or phlebotomy) or the patient died. Pneumococcal disease was defined as physician-diagnosed pneumonia, meningitis, bacteremia, sepsis, endocarditis, pleural effusion, or joint infection for which *S. pneumoniae* was identified as the etiologic agent. The specific method used to identify *S. pneumoniae* was not recorded. Diagnosis of pneumococcal otitis media or externa, pharyngitis, bronchitis, or unspecified upper respiratory tract infection did not define a case in the analysis, because these clinical conditions may be less severe and because their primary etiologic agent may be viral in patients with pneumococcal carriage. Invasive conditions included bacteremia with and without pneumonia, meningitis, sepsis, endocarditis, pleural effusion, and joint infection.

Poisson multiple regression with robust variance estimates [10] was used to determine the independent factors associated with all episodes of pneumococcal disease. Factors that were examined for a possible association with pneumococcal disease included alcoholism documented during the previous or concurrent 6-month interval; hospitalization that occurred during the previous 6-month interval; current age; the $CD4^+$ cell count (<200 cells/μL, 200–499 cells/μL, or $\geq$500 cells/μL) measured within 5 months prior to, or at the time of, observation; history of an AIDS-defining opportunistic illness (other than recurrent bacterial pneumonia); mode of HIV transmission; sex; race/ethnicity; prescription of trimethoprim-sulfamethoxazole (TMP-SMZ) and *Mycobacterium avium* complex (MAC) prophylaxis (with rifabutin, clarithromycin, or azithromycin [the antimicrobial spectrum of all 3 includes *S. pneumoniae*]) during the previous and current 6-month intervals; prescription of antiretroviral therapy (e.g., monotherapy, dual therapy, or triple-drug therapy) during the previous 6-month interval; diagnosis of pneumococcal disease during the 12 months prior to enrollment in the ASD; and administration of pneumococcal vaccine at varying $CD4^+$ cell count levels. To determine whether the risk for pneumococcal disease associated with pneumococcal vaccine status was constant for all subpopulations, we examined models stratified according to race/ethnicity, mode of HIV transmission, sex, antiretroviral therapy, and $CD4^+$ cell count.

Follow-up intervals that included a diagnosis of pneumonia caused by a pathogen other than *S. pneumoniae* or an unspecified pathogen were excluded from the risk-factor analysis, since *S. pneumoniae* could have been the cause of some of these pneumonias but may not have been detected or recorded in the medical records. Intervals that included a diagnosis of noninvasive pneumococcal disease (e.g., sinusitis, otitis, or other upper respiratory tract infection) were also excluded for the same reasons. If patients were vaccinated with pneumococcal vaccine more than once, the interval after the second vaccination was excluded. Incidence density rates were computed as the number of cases per 1000 py of follow-up.

RESULTS

During 71,116 py of observation, there were 585 episodes of pneumococcal disease (incidence rate, 8.2 episodes per 1000 py). Among these episodes, there were 474 episodes of pneumonia (with or without bacteremia; 81.0%), 110 episodes of bacteremia (18.8%), 11 episodes of meningitis (1.9%), 4 episodes of pleural effusion (0.7%), 3 episodes of joint infection (0.5%), and 2 episodes of endocarditis (0.3%). These diagnoses were not mutually exclusive. Among persons who were not vaccinated with pneumococcal vaccine, the rate of incidence of pneumococcal disease, as stratified according to recent $CD4^+$ cell counts, increased in relation to decreases in the $CD4^+$ cell count (incidence among patients with a $CD4^+$ cell count of <200 cells/μL, 12.7 episodes

per 1000 py; 200–499 cells/μL, 5.9 episodes per 1000 py; and $\geq$500 cells/μL, 1.9 episodes per 1000 py).

Characteristics of the cases, persons, and person-years included in the analysis, as well as incidence rates and results of risk-factor analysis, are summarized in table 1. The risk factors that were significantly associated with an increased risk of pneumococcal disease included injection drug use or blood transfusion as the mode of HIV transmission, black race/ethnicity, history of AIDS-related opportunistic illness, $CD4^+$ cell count of <500 cells/μL, alcoholism, recent hospitalization, and history of pneumococcal disease.

A decreased risk for pneumococcal disease was demonstrated in association with prescription of antiretroviral therapy (e.g., monotherapy, dual therapy, or triple therapy) and administration of pneumococcal vaccine when the $CD4^+$ cell count was $\geq$500 cells/μL. The risk for pneumococcal disease was not affected by the prescription of prophylaxis with TMP-SMZ for *Pneumocystis carinii* pneumonia or prophylaxis against MAC (table 1). There were no significant effects of interaction between vaccine status and other covariates included in the model.

Additional multivariate analyses were performed to examine the impact of pneumococcal vaccination on the incidence of noninvasive pneumococcal pneumonia and invasive pneumococcal disease. For noninvasive pneumococcal pneumonia (368 episodes), the incidence decreased in relation to increasing $CD4^+$ cell counts at the time of vaccination (incidence among patients with a $CD4^+$ cell count of <200 cells/μL, 6.7 episodes per 1000 py; 200–499 cells/μL, 3.3 episodes per 1000 py; and $\geq$500 cells/μL, 1.8 episodes per 1000 py; in comparison, the incidence among patients who were not vaccinated was 5.8 episodes per 1000 py). For invasive pneumococcal disease (238 episodes), a similar decrease in incidence was observed to occur in relation to an increase in the $CD4^+$ cell count at the time of vaccination (incidence among patients with a $CD4^+$ cell count of <200 cells/μL, 3.7 episodes per 1000 py; 200–499 cells/μL, 2.7 episodes per 1000 py; and $\geq$500 cells/μL, 0.8 episodes per 1000 py; in comparison, the incidence among patients who were not vaccinated was 3.8 episodes per 1000 py). However, among the additional multiple regression analyses, only the analysis of invasive disease demonstrated a statistically significant finding. Those persons who had a $CD4^+$ cell count of $\geq$500 cells/μL at the time of vaccination had a reduced risk for invasive pneumococcal disease ($P = .05$).

Of all 39,086 persons, 14,696 (37.6%) had documentation of pneumococcal vaccination in their medical records; 5144 (35%) of the 14,696 had received the vaccination within 6 months of follow-up after enrollment. No temporal trend in vaccination rates was demonstrated for these persons. Among persons in the analysis with subsequent follow-up and a known $CD4^+$ cell count at vaccination, 20.4% had been vaccinated at a $CD4^+$ cell count of $\geq$500 cells/μL. The median $CD4^+$ cell count at vaccination was 257 cells/μL (25th percentile, 82 cells/μL; 75th percentile, 452 cells/μL). Missed opportunities to vaccinate were demonstrated by the fact that only 40.2% of person-time at a $CD4^+$ cell count of $\geq$500 cells/μL (3951 persons/9821.5 py) occurred among persons who had received the vaccine.

DISCUSSION

Our study demonstrated several risk factors associated with pneumococcal disease. Among these factors was black race, since an increased risk for pneumococcal disease was found among black patients. This finding is similar to that in a nested case-control study of 85 case patients and 85 control subjects described by Gebo et al. [6], who found an increased risk of pneumococcal disease among black patients. Other investigators have also reported similar findings in studies of the general population [11–13]. Whether this increased risk is based on genetic susceptibility, socioeconomic status, or some other factor remains to be determined.

We also found that injection drug use, blood transfusion, alcoholism, recent hospitalization, and a history of pneumococcal disease within 1 year of enrollment in the ASD were associated with an increased risk for pneumococcal disease. Injection drug use has been reported to be a risk factor for bacterial pneumonia [14–18]. However, blood transfusion has not been previously reported as a mode of HIV transmission associated with an increased risk for pneumococcal disease.

Other analyses of pneumococcal disease have not assessed blood transfusion as a risk factor for disease, since too few patients with this mode of HIV transmission have been included in the study populations. However, blood transfusion is a plausible risk factor, because persons who underwent blood transfusions may have had predisposing risk factors for pneumococcal infection (e.g., renal failure or malignancy) at the time that they received HIV-infected blood [19, 20]. Previous hospitalization is probably associated with pneumococcal infection, because diseases that are recognized as risk factors for pneumococcal disease in the general population are often reasons for hospitalization [21]. Alcoholism was reported to be associated with pneumococcal infection prior to the beginning of the recognition of the HIV epidemic in the early 1980s [19, 22, 23], although it has not been consistently demonstrated to increase either the risk for pneumococcal infection [19] or the risk for bacterial pneumonia in HIV-infected persons [14]. Our study documents an increased risk for pneumococcal disease in association with the aforementioned factors in an HIV-infected population.

In our study, the incidence of pneumococcal disease decreased in association with administration of antiretroviral therapy. Gebo et al. [6] found a decreased risk for pneumococcal disease among persons who were prescribed zidovudine. These findings suggest that the effects of antiretroviral therapy are associated with a

decreased risk for pneumococcal disease as well as improved AIDS-related morbidity and mortality rates [24–26].

Our study did not demonstrate a decreased risk for pneumococcal disease in patients who were prescribed TMP-SMZ. Similar findings have been reported elsewhere [6, 16]. In one study, TMP-SMZ prophylaxis was reported to decrease the risk of confirmed cases of bacterial pneumonia by 67%; however, *S. pneumoniae* was identified in less than one-fifth of these cases of pneumonia [14]. On the basis of the results of these studies, we suspect that TMP-SMZ may prevent some episodes of bacterial pneumonia but that it is not effective for prevention of pneumococcal disease [27].

Studies of bacterial pneumonia in HIV-infected persons demonstrate that although *S. pneumoniae* is the most common cause, it is found in fewer than 20% of patients, and a pathogen is not generally identified as the cause [14, 16]. Antimicrobial resistance and lack of information on the dosage of TMP-SMZ necessary to prevent pneumococcal disease have been cited as possibly being related to the failure of TMP-SMZ to prevent pneumococcal disease [6]. In the United States, the prevalence of resistance of *S. pneumoniae* to TMP-SMZ has been reported to vary from 18% to 60% and to have increased during the past 2 decades [28–30].

We did not find a decreased risk for pneumococcal disease in association with the prescription of prophylaxis against MAC. Other studies have reported that regimens that include azithromycin and that are prescribed as prophylaxis against MAC have reduced the frequency of non-MAC bacterial infections [31, 32]. Emerging resistance to macrolides may have an impact on this benefit, especially in persons infected with penicillin-resistant organisms, since such strains have a higher prevalence of resistance to macrolides [28].

Our study demonstrated that pneumococcal vaccines that were administered when the $CD4^+$ cell count was $\geqslant$500 cells/μL produced a significantly decreased risk for pneumococcal disease among HIV-infected persons. This finding supports the recommendation to vaccinate when the patient's $CD4^+$ cell count is in this range [4]. On the basis of our study, the language in the US Public Health Service/Infectious Diseases Society of America guidelines for the prevention of opportunistic infections in persons infected with HIV could be changed to indicate that persons with a $CD4^+$ cell count of $\geqslant$500 cells/μL should "always," rather than "generally," be offered pneumococcal vaccination. This effect was not demonstrated for persons with $CD4^+$ cell counts of 200–499 cells/μL; however, the incidences of pneumococcal disease, noninvasive pneumococcal pneumonia, and invasive pneumococcal disease were lower for persons with a $CD4^+$ cell count in this range who were vaccinated, compared with those who were not vaccinated. Therefore, we suspect that vaccination may benefit some persons who have a $CD4^+$ cell count in this middle range and that it should be considered.

Administration of pneumococcal vaccine to HIV-infected persons is supported by the following factors: it is inexpensive and cost-effective [33], and it covers the majority of pneumococcal serogroups that cause pneumococcal bacteremia [34]. It is of increased importance to vaccinate HIV-infected persons, given the reported increases in antibiotic-resistant *S. pneumoniae* [4]. In addition, HIV-infected persons have many of the risk factors for acquisition of drug-resistant *S. pneumoniae* infections, including infection with HIV, recent antimicrobial therapy, coexisting illness or underlying disease, immunodeficiency, and recent or current hospitalization [28].

We found that rates of vaccination were very low and had not increased during the study period. A low level of pneumococcal vaccination among the general US population has also been reported [35]. We hypothesize that this is due to several factors, including the reimbursement practices of some insurance payers, the lack of significant advertising or public health campaigns that advocated pneumococcal vaccination in the 1990s, the absence of a controlled clinical trial that demonstrates the efficacy of the vaccine in HIV-infected persons, and concern about vaccine-associated adverse reactions that occur after revaccination as well as observations of increased virus load [3, 35–39].

However, pneumococcal vaccine has not been demonstrated to cause long-lasting changes in virus load [40, 41]. In our study, the median $CD4^+$ cell count at the time of pneumococcal vaccination was 276 cells/μL. Therefore, many patients who receive the vaccine are undergoing vaccination when the immune system has impaired antibody responses [3, 42, 43]. Our study supports vaccination that is done early during the course of HIV infection, and it underscores the need to identify HIV-infected persons as early as possible and to provide them with care.

Among the limitations of our study is the fact that the ASD does not involve population-based surveillance. As a result, the findings of our study might not be generalizable to all HIV-infected adults and adolescents who receive care in the United States. However, the ASD is large and diverse, and it has enrolled thousands of HIV-infected persons since its inception. Because the ASD is a surveillance study that involves the abstraction of data from medical records, it relies on documentation by health care providers and their staff for completeness of information. We cannot be certain that pneumococcal vaccination is routinely recorded in the medical records, and our rates of vaccination thus may be lower than the true rates.

The initial data abstraction in the ASD is a 12-month retrospective review of the medical records for most conditions, and it includes review of pneumococcal vaccination. Some patients could have been vaccinated prior to this 12-month period. However, many patients enrolled in the ASD are beginning

Table 1. Characteristics, incidence, and results of multivariate Poisson regression analysis done to determine the independent risk factors associated with pneumococcal disease among HIV-infected persons.

Characteristic	No. of episodes	No. of persons	No. of py	Incidence, no. of episodes per 1000 py	RR (95% CLs)	*P*
Overall	585	39,086	71,119	8.2	—	—
Sex						
Male	448	31,563	57,107	7.8	0.9 (0.6, 1.1)	.25
Female	137	7523	14,009	9.8	Referent	NA
Age, y						
13–19	2	529	549	3.6	NA	NA
20–29	109	9897	13,363	8.2	NA	NA
30–39	273	21,549	33,236	8.2	NA	NA
40–49	158	11,418	18,287	8.6	NA	NA
50–59	32	2908	4610	6.9	NA	NA
⩾60	11	662	1071	10.3	NA	NA
Linear trend for age, y	NA	NA	NA	NA	1.0 (0.9, 1.1)	.47
Mode of HIV transmission						
Male-male sex	225	18,832	36,402	6.2	Referent	NA
Injection drug use	244	11,144	19,221	13.0	1.5 (1.2, 1.9)	<.01
Heterosexual contact	39	3694	7034	5.5	1.0 (0.6, 1.6)	.90
Hemophilia	4	184	365	11.0	1.7 (0.6, 4.6)	.27
Blood transfusion	12	524	920	13.1	2.0 (1.1, 3.9)	.03
Race/Ethnicity						
White	208	15,517	30,523	6.8	Referent	NA
Black	322	15,969	27,229	11.8	1.5 (1.2, 1.9)	<.01
Hispanic	49	7142	12,452	3.9	0.7 (0.5, 1.1)	.10
Asian/Pacific Islander	1	287	565	1.8	0.4 (0.1, 2.7)	.33
Native American	5	171	348	14.4	1.0 (0.4, 2.5)	.97
History of AIDS-defining OI						
Yes	332	18,288	22,974	14.5	2.1 (1.7, 2.5)	<.01
No	253	29,399	48,142	5.3	Referent	NA
Recent $CD4^+$ cell count, cells/μL						
<200	308	22,726	26,318	11.7	3.7 (2.2, 6.3)	<.01
200–499	101	17,746	19,170	5.3	2.5 (1.5, 4.2)	<.01
⩾500	19	9882	9822	1.9	Referent	NA
Alcoholism						
Yes	149	6753	6967	21.4	2.0 (1.7, 2.5)	<.01
No	436	36,986	64,149	6.8	Referent	NA
Hospitalized during previous 6-month interval						
Yes	228	16,307	10,953	20.8	2.1 (1.7, 2.5)	< .01
No	357	34,961	60,163	5.9	Referent	NA
Pneumococcal disease within 1 y of enrollment in study						
Yes	34	184	266	128.1	8.6 (5.1, 14.5)	<.01
No	551	38,902	70,851	7.8	Referent	NA
Prophylaxis with TMP-SMZ						
Yes	215	15,289	19,390	11.1	1.2 (0.9, 1.4)	.16
No	370	34,175	51,726	7.2	Referent	NA

(continued)

Table 1. Continued

Characteristic	No. of episodes	No. of persons	No. of py	Incidence, no. of episodes per 1000 py	RR (95% CLs)	*P*
Prophylaxis with rifabutin, clarithromycin, or azithromycin						
Yes	31	3504	3228	9.6	0.9 (0.6, 1.4)	.78
No	554	39,040	67,888	8.2	Referent	NA
Antiretroviral therapy						
None	264	26,926	27,930	9.5	Referent	NA
With 1 drug	206	22,036	26,440	7.8	0.6 (0.5, 0.8)	<.01
With 2 drugs	78	11,218	10,415	7.5	0.7 (0.6, 1.0)	.05
With 3 drugs	26	5780	5164	5.0	0.5 (0.3, 0.9)	.01
Pneumococcal vaccination, $CD4^+$ cells/μL at time of vaccination						
Not administered	399	38,068	43,100	9.3	Referent	NA
<200	79	5498	7895	10.0	1.0 (0.7, 1.4)	.99
200–499	64	4872	10,843	5.9	1.0 (0.8, 1.4)	.85
⩾500	16	2663	6206	2.6	0.5 (0.3, 0.9)	.02

NOTE. CLs, confidence limits; NA, not applicable; OI, opportunistic illness; py, person-years of observation; TMP-SMZ, trimethoprim-sulfamethoxazole.

to receive care for HIV disease and are unlikely to have received pneumococcal vaccine in the past. The rate of vaccination found in our study was similar to the low rates described in other populations [35].

Our study did not address patient adherence to medications, such as prophylaxis or antiretroviral agents, nor did it collect exact dates or reasons why medications were chosen. The ASD is able to monitor only prescription of medications. Finally, these data were derived from an observational database and not from a prospective clinical trial. Although our findings may not carry the same weight as the results of a clinical trial of pneumococcal vaccine in HIV-infected persons, there are no data from US clinical trials that are available for comparison.

In conclusion, we emphasize heightened awareness of the potential value of pneumococcal vaccine, and we recommend that it be administered to HIV-infected persons early in the course of HIV infection, before profound immunosuppression has occurred. It remains to be determined whether pneumococcal vaccine should be withheld from HIV-infected antiretroviral-naive persons with a $CD4^+$ cell count of <500 cells/μL until antiretroviral therapy has been administered and the $CD4^+$ cell count has been boosted.

Acknowledgments

We gratefully acknowledge the administrative assistance of Scott B. McCombs, the database management performed by Pei-Chun T. Wan and Michael Adams (for the ASD), and the review of the manuscript by Anne Schuchat.

APPENDIX

ASD investigators (locations): Melanie Thompson and Julia Gable (AIDS Research Consortium of Atlanta); Sylvia Odem and Dr. Sharon Melville (Texas Department of Health, Austin); Drs. Arthur Davidson, David L. Cohn, and Cornelius Rietmeijer (Denver Department of Health and Hospitals); Dr. Linda L. Wotring and Eve D. Mokotoff (Michigan Department of Community Health, Detroit); Wes McNeely and Kaye Reynolds (Houston Department of Health and Human Services); Dr. Frank Sorvillo, Jane Turner, and Dorothy Masters (Los Angeles County Department of Health Services); Stephanie Broyles and Anne Morse (Louisiana Office of Public Health, New Orleans); Dr. Judy Sackoff (The City of New York Department of Health); Jose Otero, and Drs. Robert Hunter and Maria de los Angeles Gomez (University Central del Caribe, Bayamon, Puerto Rico); Sandra Miranda (Puerto Rico Department of Health, San Juan); and Beth Sohlberg, and Drs. Susan Buskin and Sharon G. Hopkins (Seattle–King County Department of Public Health).

References

1. Bartlett JG. Pneumonia in the patient with HIV infection. Infect Dis Clin North Am **1998**; 12:807–20.
2. Mundy LM, Auwaerter PG, Oldach D, et al. Community-acquired pneumonia: impact of immune status. Am J Respir Crit Care Med **1995**; 152:1309–15.
3. Janoff EN, Breiman RF, Daley CL, Hopewell PC. Pneumococcal disease during HIV infection. Ann Intern Med **1992**; 117:314–24.
4. Centers for Disease Control and Prevention. 1999 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected

with human immunodeficiency virus: US Public Health Service (USPHS) and Infectious Diseases Society of America (IDSA). MMWR Morb Mortal Wkly Rep **1999**; 48(RR-10):1–59; 61–6.
5. Ward JW, Hanson DL, Jones JL, Kaplan J. Pneumococcal vaccination and the incidence of pneumonia among HIV-infected persons [abstract 245]. In: Program and abstracts of the 34th Annual Meeting of the Infectious Diseases Society of America. Alexandria, Virginia: Infectious Diseases Society of America, **1996**.
6. Gebo KA, Moore RD, Keruly JC, Chaisson RE. Risk factors for pneumococcal disease in human immunodeficiency virus–infected patients. J Infect Dis **1996**; 173:857–62.
7. Farizo KM, Buehler JW, Chamberland ME, et al. Spectrum of disease in persons with human immunodeficiency virus infection in the United States. JAMA **1992**; 267:1798–805.
8. Dworkin MS, Wan PCT, Hanson DL, Jones JL, the Adult and Adolescent Spectrum of HIV Disease Project. Progressive multifocal leukoencephalopathy: improved survival of HIV-infected patients in the protease inhibitor era. J Infect Dis **1999**; 180:621–5.
9. Centers for Disease Control and Prevention. 1993 Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR Morb Mortal Wkly Rep **1992**; 41(RR-17):1–19.
10. Liang KY, Zeger SL. Longitudinal data analysis using generalized linear models. Biometrika **1986**; 73:13–22.
11. Brieman RF, Spika JS, Navarro VJ, Darden PM, Darby CP. Pneumococcal bacteremia in Charleston County, South Carolina: a decade later. Arch Intern Med **1990**; 150:1401–5.
12. Schuchat A, Robinson KA, Wenger JD, et al. Bacterial meningitis in the United States in 1995. N Engl J Med **1997**; 337:970–6.
13. Schuchat A, Broome CV, Hightower AW, Costa S, Parkin W. Use of surveillance for invasive pneumococcal disease to estimate the size of the immunosuppressed HIV-infected population. JAMA **1991**; 265:3275–9.
14. Hirschtick RE, Glassroth J, Jordan MC, et al. Bacterial pneumonia in persons infected with the human immunodeficiency virus. N Engl J Med **1995**; 333:845–51.
15. Caiaffa WT, Vlahov D, Graham NM, et al. Drug smoking, *Pneumocystis carinii* pneumonia, and immunosuppression increase risk of bacterial pneumonia in human immunodeficiency virus–seropositive injection drug users. Am J Respir Crit Care Med **1994**; 150:1493–8.
16. Tumbarello M, Tacconelli E, de Gaetano K, et al. Bacterial pneumonia in HIV-infected patients: analysis of risk factors and prognostic indicators. J Acquir Immune Defic Syndr Hum Retroviol **1998**; 18:39–45.
17. Mientjes GHC, Spijkerman IJB, Ameijden EJC, van den Hoek JAR, Coutinho RA. Incidence and risk factors for pneumonia in HIV infected and non-infected drug users. J Infect **1996**; 32:181–6.
18. Boschini A, Smacchia C, Di Fine M, et al. Community-acquired pneumonia in a cohort of former injection drug users with and without human immunodeficiency virus infection: incidence, etiologies, and clinical aspects. Clin Infect Dis **1996**; 23:107–13.
19. Lipsky BA, Boyko EJ, Inui TS, et al. Risk factors for acquiring pneumococcal infections. Arch Intern Med **1986**; 146:2179–85.
20. Afessa B, Greaves WL, Frederick WR. Pneumococcal bacteremia in adults: a 14-year experience in an inner-city university hospital. Clin Infect Dis **1995**; 21:345–51.
21. Fedson DS, Chiarello LA. Previous hospital care and pneumococcal bacteremia: importance for pneumococcal immunization. Arch Intern Med **1983**; 143:885–9.
22. Brayton RG, Stokes PE, Schwartz MS, et al. Effect of alcohol and various diseases on leukocyte mobilization, phagocytosis, and intracellular bacterial killing. N Engl J Med **1970**; 282:123–8.
23. Burman LA, Norrby R, Trollfors B. Invasive pneumococcal infections: incidence, predisposing factors, and prognosis. Rev Infect Dis **1985**; 7: 133–42.
24. McNaghten AD, Hanson DL, Jones JL, Dworkin MS, Ward JW, and the Adult/Adolescent Spectrum of Disease Group. Effects of antiretroviral therapy and opportunistic illness primary chemoprophylaxis on survival after AIDS diagnosis. AIDS **1999**; 13:1687–95.
25. Palella FJ, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. N Engl J Med **1998**; 338:853–60.
26. Jones JL, Hanson DL, Dworkin MS, et al. Surveillance for AIDS-defining opportunistic illnesses, 1992–1997. MMWR Morb Mortal Wkly Rep **1999**; 48(SS-2):1–22.
27. Tumbarello M, Tacconelli E, Cauda R, Ortona L. Secondary *Pneumocystis carinii* pneumonia prophylaxis with trimethoprim-sulfamethoxazole does not prevent bacterial pneumonia in HIV-infected persons. AIDS **1996**; 10:1603–4.
28. Campbell GD Jr, Silberman R. Drug-resistant *Streptococcus pneumoniae.* Clin Infect Dis **1998**; 26:1188–95.
29. Fairchok MP, Ashton WS, Fischer GW. Carriage of penicillin-resistant pneumococci in a military population in Washington, DC: risk factors and correlation with clinical isolates. Clin Infect Dis **1996**; 22:966–72.
30. Doern GV, Brueggemann A, Holley HP Jr, Rauch AM. Antimicrobial resistance of *Streptococcus pneumoniae* recovered from outpatients in the United States during the winter months of 1994 to 1995: results of a 30-center national surveillance study. Antimicrob Agents Chemother **1996**; 40:1208–13.
31. Havlir DV, Dube MP, Sattler FR, et al. Prophylaxis against *Mycobacterium avium* complex with weekly azithromycin, daily rifabutin, or both. N Engl J Med **1996**; 335:392–8.
32. Oldfield III EC, Fessel WJ, Dunne MW, et al. Once weekly azithromycin therapy for prevention of *Mycobacterium avium* complex infection in patients with AIDS: a randomized, double-blind, placebo-controlled multicenter trial. Clin Infect Dis **1998**; 26:611–9.
33. Rose DN, Schechter CB, Sacks HS. Influenza and pneumococcal vaccination of HIV-infected patients: a policy analysis. Am J Med **1993**; 94:160–8.
34. Hibbs JR, Douglas JM Jr, Judson FN, McGill WL, Rietmeijer CA, Janoff EN. Prevalence of human immunodeficiency virus infection, mortality rate, and serogroup distribution among patients with pneumococcal bacteremia at Denver General Hospital 1984–1994. Clin Infect Dis **1997**; 25:195–9.
35. Fedson DS. Pneumococcal vaccination in the United States and 20 other developed countries, 1981–1996. Clin Infect Dis **1998**; 26:1117–23.
36. Rushton TC, Ganguly R, Sinnott JT 4th, Banerji M. Barriers to immunization: an examination of factors that influence the application of pneumococcal vaccine by house staff. Vaccine **1994**; 12:1173–9.
37. Hilleman MR, Carlson AJ Jr, McLean AA, Vella PP, Weibel RE, Woodhour AF. *Streptococcus pneumoniae* polysaccharide vaccine: age and dose responses, safety, persistence of antibody, revaccination, and simultaneous administration of pneumococcal and influenza vaccines. Rev Infect Dis **1981**; 3(Suppl):S31–42.
38. Vigano A, Bricalli D, Trabattoni D, et al. Immunization with both T cell–dependent and T cell–independent vaccines augments viral load. AIDS Res Hum Retroviruses **1998**; 14:727–34.
39. Brichacek B, Swindells S, Janoff EN, Pirruccello S, Stevenson M. Increased plasma human immunodeficiency virus type 1 burden following antigenic challenge with pneumococcal vaccine. J Infect Dis **1996**; 174:1191–9.
40. Katzenstein TL, Gerstoft J, Nielsen H. Assessments of plasma HIV RNA and CD4 cell counts after combined Pneumovax and tetanus toxoid vaccination: no detectable increase in HIV replication 6 weeks after immunization. Scand J Infect Dis **1996**; 28:239–41.
41. Kroon FP, van Furth R, Bruisten SM. The effects of immunization in human immunodeficiency virus type 1 infection. N Engl J Med **1996**; 335:817–9.
42. Janoff EN, Douglas JM Jr, Gabriel M, et al. Class-specific antibody response to pneumococcal capsular polysaccharides in men infected with human immunodeficiency virus type 1. J Infect Dis **1988**; 158:983–90.
43. Ammann AJ, Schiffman G, Abrams D, Volberding P, Ziegler J, Conant M. B-cell immunodeficiency in acquired immune deficiency syndrome. JAMA **1984**; 251:1447–9.