Colonization by *Streptococcus pneumoniae* among Human Immunodeficiency Virus–Infected Adults: Prevalence of Antibiotic Resistance, Impact of Immunization, and Characterization by Polymerase Chain Reaction with BOX Primers of Isolates from Persistent *S. pneumoniae* Carriers

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Pharyngeal colonization by *Streptococcus pneumoniae* was evaluated in 103 human immunodeficiency virus (HIV)–infected subjects (<200 CD4 cells/μL, 57; ≥200 CD4 cells/μL, 46) and 39 non–HIV-infected controls who were participants in a vaccine study. At baseline, 7%, 20%, and 10% of subjects in the <200 and ≥200 CD4 cell groups and in the control group were colonized with *S. pneumoniae*: Rates at 6 months were 23%, 22%, and 6%, respectively. Of 34 isolates from HIV-infected subjects, 25 were penicillin-resistant and 19 were resistant to ≥3 antimicrobials; of 8 isolates from controls, 1 was resistant. Resistance to trimethoprim-sulfamethoxazole was significantly higher among HIV-infected subjects with <200 CD4 cells/μL than in those with more CD4 cells. Polymerase chain reaction DNA analysis with BOX primers demonstrated that 12 HIV-infected subjects were persistently colonized with the same *S. pneumoniae* strain for ≥1 month compared with none of the controls. HIV-infected subjects were more likely to be persistent pneumococcal carriers and to carry antibiotic-resistant isolates than were non–HIV-infected subjects.

Persons infected with human immunodeficiency virus (HIV) are estimated to be >100 times more susceptible to invasive pneumococcal disease than an age-matched, non–HIV-infected population [1, 2]. They usually present with pneumonia, which in ~50% of cases is accompanied by bacteremia [3]. Host-defense defects associated with this predisposition include abnormalities in the antibody response to natural infection and immunization [4–7]. Infection with pneumococcal disease in otherwise healthy adults appears to depend in part on the frequency with which invasive serotypes are carried in the nasopharynx [8]; such carriage varies widely within populations. In a cross-sectional study, Janoff et al. [4] examined pneumococcal colonization in HIV-infected homosexual males and found that HIV infection did not appear to predispose to an increased carriage rate.

Resistance of *Streptococcus pneumoniae* to penicillin and other antibiotics is increasing worldwide [9]. In the United States, drug-resistant pneumococcal infections appear to be more common among children than adults [10, 11], especially in children attending day care centers [12–14]. Recent studies suggest that HIV infection is a risk factor for recovery of penicillin-resistant *S. pneumoniae* from persons with invasive pneumococcal disease [15–17]; however, the prevalence of colonization with antibiotic-resistant *S. pneumoniae* in HIV-infected persons is not known.

Serotyping has been the principal means of distinguishing *S. pneumoniae* isolates. Other methods for subtyping include penicillin-binding protein electrophoretic patterns [18–20], surface protein A typing [19], multilocus enzyme electrophoresis [18–21], and molecular biologic techniques, such as ribotyping [22, 23], pulsed-field gel electrophoresis [20], and DNA analysis using polymerase chain reaction (PCR) technology [18, 19, 21, 23]. Recently, an interspersed repetitive DNA sequence, the BOX element, was identified from *S. pneumoniae* [24]. Among different techniques for molecular typing of *S. pneumoniae*, DNA analysis based on the BOX element has some of the best discriminatory potential [25–27].

Our objective was to compare pneumococcal pharyngeal colonization in HIV-infected men stratified by CD4 cell count to that in age-matched controls. We also assessed the prevalence of antibiotic resistance among colonizing isolates, evaluated the effect of vaccination on carriage rate, and used repetitive element PCR with BOX primers to evaluate consecutive strains from persistent pneumococcal carriers.
Subjects and Methods

Subjects. Subjects were participants in a prospective, randomized trial in which a pentavalent protein conjugate pneumococcal vaccine was evaluated in HIV-infected adults [7]. HIV-infected patients were recruited from the Houston VA Medical Center and stratified by CD4 cell count (≥200 or <200 cells/μL). Controls were healthy employees with negative serology or no known risk factors for HIV infection. Subjects were recruited from July to December 1994. To avoid seasonal bias, proportional numbers of HIV-infected and control subjects were enrolled each month. Subjects with a history of pneumococcal immunization or documented pneumococcal infection in the preceding 5 years were excluded, as were those with an acute infection. Prior or current antimicrobial use was not an exclusion criterion for enrollment in the colonization study. Antibiotic use among HIV-infected subjects was assessed by self-reporting and by review of computerized pharmacy records; in the control group, this information was based solely on self-reporting. At baseline evaluation, subjects were randomized to receive 23-valent pneumococcal polysaccharide vaccine (Pnu-immune; Lederle Laboratories, Pearl River, NY) or a pentavalent protein-conjugate vaccine containing serotypes 6B, 14, 18, 19F, and 23F conjugated to CRM197, a nontoxic mutant diphtheria toxin (Lederle). Subjects had 1- and 6-month evaluations; at 6 months they were offered the alternate vaccine. Patients who were revaccinated had a 7-month evaluation. Results of the immunogenicity of the vaccine are published elsewhere [7].

Isolation and identification of S. pneumoniae. At each visit, subjects had swabs (Culturette; Becton Dickinson Microbiology Systems, Cockeysville, MD) of their posterior pharynx and tonsils (if present). Within 4 h, the sample was inoculated onto trypticase-soy agar plates supplemented with 5% sheep’s blood with gentamicin (2.5 mg/L) and incubated at 37°C with 5% CO2 for 24–48 h. α-hemolytic colonies with morphology suggestive of S. pneumoniae were streaked on blood agar, and an optochin disk (Difco Laboratories, Detroit) was placed on the surface before incubation. Strains that exhibited an inhibition zone ≥14 mm around the optochin disk and were bile-soluble were identified as S. pneumoniae. Identification was confirmed in all isolates by a culture identification test (AccuProbe; GenProbe, San Diego). S. pneumoniae isolates were serotyped by agglutination with type-specific antisera (Statens Seruminstitut, Copenhagen).

Antimicrobial susceptibility of S. pneumoniae. Screening for penicillin susceptibility was done with oxacillin disks (Difco). MICs of penicillin and cefotaxime were determined using E-test strips (AB Biodisk, Culver City, CA). Susceptibility to trimethoprim-sulfamethoxazole, chloramphenicol, erythromycin, and tetracycline (Difco) was determined by the disk diffusion method following the guidelines and definitions of the National Committee for Clinical Laboratory Standards as recommended by the Centers for Disease Control and Prevention [28].

BOX-PCR. PCR, based on BOXA1R oligonucleotide primers [26], was done using whole-cell suspensions as template material. Bacterial colonies were suspended and washed once in 1 mL of 1 M NaCl, washed again in distilled water, and resuspended in distilled water to a final concentration of 107–108 cfu/mL. Each 25-μL PCR reaction contained 2 μL of bacterial suspension, 1.25 mM each of 4 dNTPs, 50 μM primer, and 2 U of AmpliTaq DNA polymerase in a buffer with 10% dimethyl sulfoxide (vol/vol). Precautions for avoiding contamination of the reaction mixture were strictly followed [29]. Negative controls (sample with reagents but no bacterial DNA template) were included in each assay. PCR amplifications were done in an automated thermal cycler (Perkin-Elmer Cetus, Norwalk, CT) with an initial melt of 80°C for 15 min, followed by denaturation at 95°C for 7 min, 30 denaturation cycles at 90°C, 30 s; annealing at 52°C, 1 min; extension of 65°C, 8 min; and a single final extension at 65°C, 16 min. Each PCR product (7 μL) was electrophoresed on a 1% agarose gel at 100 V for 2.5 h in 1× TBS Tris–EDTA buffer and stained with 0.5 mg/mL ethidium bromide. Agarose gels were visualized and photographed under UV transillumination.

Statistical analysis. For each time period, colonization rates among all 3 groups and rates of acquisition and persistence were compared by χ2 test. Two-group comparisons of proportions were made using Fisher’s exact test. Within each group, longitudinal changes in colonization rates were assessed by McNemar’s test for correlated proportions. The effect of different variables on colonization by time period was tested by logistic regression analysis. Unpaired Student’s t test was used for comparison of continuous variables.

Results

Subject characteristics. In total, 103 HIV-infected subjects and 39 non–HIV-infected controls were enrolled in the study. Mean ages were similar in HIV-infected subjects and controls (42 ± 9 and 39 ± 11 years, respectively). Risk factors for HIV infection were homosexuality in 59% and intravenous drug use in 23% of the subjects. HIV-infected subjects were more likely than controls to be smokers (63% vs. 27%, P < .05) and to have received antibiotics in the previous 6 months (70% vs. 5%, P < .05), while controls were more likely to have children ≤5 years old in the household (24% vs. 8%, P < .05). The proportion of subjects who had baseline and 1- and 6-month evaluations during winter months (December, January, February, March) was similar for controls and HIV-infected subjects (10%, 10%, and 50% and 4%, 5%, and 40%, respectively). Significantly more controls had 7-month evaluations during winter months (50% vs. 20%, P < .05). Among HIV-infected subjects, there were no differences between those with <200 or ≥200 CD4 cells/μL, respectively, in mean age (42 ± 8 vs. 42 ± 9 years), intravenous drug use (21% vs. 24%), smoking (62% vs. 65%), or children ≤5 years old in the household (9% vs. 6%). However, at enrollment, those with <200 CD4 cells/μL were more likely than were persons with more CD4 cells to be receiving trimethoprim-sulfamethoxazole (81% vs. 15%, P < .05) or another antibiotic in addition to trimethoprim-sulfamethoxazole (30% vs. 13%, P < .05), to have received any antibiotic in the prior 6 months (88% vs 52%, P < .05), and to have received a greater number of different antimicrobials in the prior 6 months (2.5 ± 1.3 vs. 1.5 ± 1.2, P < .05).

Carriage. HIV-infected subjects with ≥200 CD4 cells/μL tended to have higher carriage rates than persons with fewer infections with S. pneumoniae.
Table 1. Carriage rate of *S. pneumoniae* among HIV-infected subjects and controls at each time period.

<table>
<thead>
<tr>
<th>Visit</th>
<th>Controls</th>
<th>CD4 cells/µL</th>
<th>CD4 cells/µL</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>≥200</td>
<td>&lt;200</td>
</tr>
<tr>
<td>Baseline</td>
<td>4/39 (10)</td>
<td>9/46 (20)</td>
<td>4/57 (7)</td>
</tr>
<tr>
<td>1 month</td>
<td>2/39 (5)</td>
<td>7/41 (17)</td>
<td>6/51 (12)</td>
</tr>
<tr>
<td>6 month</td>
<td>0/38</td>
<td>8/35 (23)*</td>
<td>8/37 (22)*</td>
</tr>
<tr>
<td>7 month</td>
<td>2/34 (6)</td>
<td>5/25 (20)</td>
<td>7/29 (25)</td>
</tr>
</tbody>
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NOTE. Data are no. of carriers/no. of subjects evaluated at visit (%).

* P < .05 vs. controls (χ²).

CD4 cells and controls (not significant) at baseline and at 1 month follow-up. At 6 months, both groups of HIV-infected subjects carried pneumococci significantly more frequently than controls (*P* < .05; table 1). Throughout the study period, the carriage rate was stable in HIV-infected subjects with ≥200 CD4 cells/µL (17%–23%). An increase in carriage was observed among subjects with <200 CD4 cells/µL, rising from 7% at baseline to 22% at the 6-month evaluation (not significant).

For analysis of acquisition of pneumococci, loss of carriage state, and persistence of carriage, results were analyzed for patients who had 2 consecutive samples obtained at any of three intervals: months 0–1, 1–6, and 6–7 (table 2). HIV-infected persons were more likely to acquire and less likely to lose the carrier state and thus were more likely to be persistent carriers. Of the 18 HIV-infected pneumococcal carriers who had ≥1 evaluation after they were found to be colonized, 14 (7 each with ≥200 and <200 CD4 cells/µL) were colonized for ≥1 month compared with 1 of 5 controls (*P* < .05). Of the 14 HIV-infected persistent carriers, 5 were colonized ≥6 months (2 had <200 and 3 had ≥200 CD4 cells/µL).

### Serotypes

There were no significant differences between HIV-infected persons and controls in the prevalence of any pneumococcal serotype. The most frequently isolated serotypes were 6 and 14 (5 and 4 subjects, respectively); serotypes 8, 19, and 22 (3 subjects each); and serotypes 1, 9, 12, and 18 (2 subjects each). All control subjects and 72% of HIV-infected subjects with ≥200 CD4 cells/µL and 71% with <200 CD4 cells/µL carried serotypes that are in the polysaccharide vaccine. For the respective 3 groups, fewer subjects carried protein-conjugate vaccine serotypes (57%, 22%, and 36%; *P* < .05 only for subjects with ≥200 vs. CD4 cells/µL). Among HIV-infected subjects, 16% of carriers were colonized with nontypeable isolates compared with no controls.

#### Antimicrobial susceptibility

Among subjects with <200 CD4 cells/µL, 11 (79%) of the 14 carriers were colonized with isolates resistant to trimethoprim-sulfamethoxazole. All 11 were receiving this drug combination. In addition, 64% of the isolates were resistant to penicillin, 71% were resistant to erythromycin, and 71% were resistant to tetracycline (table 3). The majority (85%) of isolates from subjects with ≥200 CD4 cells/µL were susceptible to trimethoprim-sulfamethoxazole; however, 80% were resistant to penicillin, 80% to tetracycline, and 90% to erythromycin. Among penicillin-resistant isolates, 2 (serotypes 6 and 18) were highly resistant and also resistant to cefotaxime. Of the isolates from the HIV-infected patients, none was fully susceptible, 1 was resistant only to penicillin, and 1 was resistant only to trimethoprim-sulfamethoxazole. Six isolates resistant to trimethoprim-sulfamethoxazole. All 11 subjects were receiving this drug combination. In addition, 64% of the isolates were resistant to penicillin, 71% were resistant to erythromycin, and 71% were resistant to tetracycline (table 3). The majority (85%) of isolates from subjects with ≥200 CD4 cells/µL were susceptible to trimethoprim-sulfamethoxazole; however, 80% were resistant to penicillin, 80% to tetracycline, and 90% to erythromycin. Among penicillin-resistant isolates, 2 (serotypes 6 and 18) were highly resistant and also resistant to cefotaxime. Of the isolates from the HIV-infected patients, none was fully susceptible, 1 was resistant only to penicillin, and 1 was resistant only to trimethoprim-sulfamethoxazole.
of the 14 isolates from subjects with <200 CD4 cells/μL and 13 of 19 from subjects with ≥200 CD4 cells/μL were resistant to ≥2 antimicrobials. Among isolates from controls, 1 (13%) of 8 was resistant to penicillin (serotype 14, which was also resistant to erythromycin and tetracycline) and 1 each was resistant to tetracycline and to trimethoprim-sulfamethoxazole.

Risk factors for pneumococcal colonization. Among the HIV-infected subjects at each time period, CD4 cell counts were similar among colonized and noncolonized subjects. By logistic regression analysis, history of intravenous drug use, and type of vaccine at enrollment were not significantly associated with colonization. There were not enough ties in specific IgA responses, the immunoglobulin associated with mucosal immunity, after pneumococcal immunization include decreased numbers of IgA antibody–secreting cells and diminished serum levels of antcapsular IgA [33]. Abnormalities in secretory IgA2, the IgA responsible for recognition of polysaccharide antigens at the mucosal level, have also been described [34], although a relationship between pneumococcal bacteremia and selective IgA2 deficiency in HIV infection has not been demonstrated [35]. The role of these defective re-

Effect of immunization. One month after initial vaccination, the 4 controls who carried S. pneumoniae (serotypes 4, 6, 8, and 14) cleared the organisms; all but 1 subject (no. 98) had received protein-conjugate vaccine. Subject 98 was colonized at 1 month by another vaccine serotype (serotype 14); he had adequate antibody responses after immunization to serotypes 6 and 14 (>4-fold increases in IgG postimmunization titers). At the 6-month follow-up visit, there were no carriers in the control group, but at the 7-month visit, 2 subjects not previously colonized carried vaccine serotypes 6 and 19. Two of the 3 subjects who acquired new organisms during the study (including subject 98) had children <5 years old in their households.

Among the HIV-infected subjects, neither vaccine reduced colonization rates nor prevented their becoming carriers. The baseline colonization rate was similar among patients who received the polysaccharide and protein-conjugate vaccines (10% and 15%, respectively). At 1- and 6-month evaluations, the colonization rates were 15% (7 of 47) and 27% (10 of 37) among those given the protein-conjugate vaccine and 13% (6 of 45) and 17% (6 of 35) among polysaccharide vaccine recipients, respectively. These rates were not significantly different. Of the 14 persistent carriers, 8 initially received protein-conjugate vaccine and 6 received polysaccharide vaccine. In these carriers (as in the whole cohort) [7], antibody responses to the 5 pneumococcal polysaccharides in the protein-conjugate vaccine were relatively low. The majority of subjects (8 of 14) had ≥2-fold increases in postimmunization IgG titers to ≤2 of the 5 antigens tested. The low number of carriers in each vaccine group precluded deriving meaningful conclusions from additional comparisons.

BOX-PCR characterization of isolates from persistent carriers. Fifteen of 18 HIV-infected subjects and 1 of 5 controls were colonized by S. pneumoniae on ≥1 occasion and were classified as persistent carriers. Isolates from 3 patients were not available for further evaluation. The 33 pneumococcal isolates from the remaining 13 subjects were analyzed by BOX-PCR. These isolates were serotypes 6, 9, 11, 14, 19, 22, and 25. Isolates from 5 subjects were nontypeable. BOX-PCR yielded distinct DNA patterns (figure 1) and showed that 11 of the 13 persistent carriers were colonized by the same strain more than once. Three subjects (including the only control) were colonized by ≥1 strain; 2 subjects (nos. 98 and 291) lost their original serotype and acquired a new one within a 1-month period.

Of the 5 subjects who were carriers ≥6 months, 4 carried the same strain (subjects 282, 310, 495, 517). Subject 298 carried the same strain ≥1 month but was colonized by a different strain at the 6-month evaluation. Subject 505 had the same strain at baseline and at the 6-month evaluation, but his throat culture at the 1-month study was negative. Thus, he may have lost and reacquired the same isolate, perhaps from the same contact, or he may have been a persistent carrier and the organism was missed at his second visit. Five subjects were colonized by nontypeable S. pneumoniae. BOX-PCR showed that 3 (nos. 473, 502, and 505) were colonized by unique strains.

Strains in 2 pairs of subjects were indistinguishable by BOX-PCR DNA analysis. Subjects 291 and 298 carried serotype 22 and subjects 282 and 310 carried serotype 9. At present, we do not know if BOX-PCR will differentiate strains for all pneumococcal serotypes, since only a limited number of serotypes and isolates have been tested with this method [23, 25–27, 30]. Serotype 9V isolates appear to be genetically closely related when evaluated by BOX-PCR [30] and other genotypic methods (multilocus enzyme electrophoresis and pulsed-field gel electrophoresis) [31]. Data are not available for serotype 22.

Discussion

HIV-infected persons appear to have an increased rate of pharyngeal colonization by S. pneumoniae. The carriage rate among HIV-infected subjects with >200 CD4 cells/μL (17%–23%), most of whom were not receiving prophylactic antibiotics, was higher than the 5% previously found in adults without children [32] and the 14% reported in HIV-infected adults [4]. HIV infection causes defective humoral responses to pneumococcal infection [4, 5] and immunization [3, 6, 7]. Abnormalities in specific IgA responses, the immunoglobulin associated with mucosal immunity, after pneumococcal immunization include decreased numbers of IgA antibody–secreting cells and diminished serum levels of antcapsular IgA [33]. Abnormalities in secretory IgA2, the IgA responsible for recognition of polysaccharide antigens at the mucosal level, have also been described [34], although a relationship between pneumococcal bacteremia and selective IgA2 deficiency in HIV infection has not been demonstrated [35]. The role of these defective re-
more likely to be carriers than were those without children, but the difference was not significant.

Factors unrelated to HIV infection may contribute to the increased carriage rate we observed. In vitro studies suggest that smoking may enhance adherence by S. pneumoniae to buccal epithelial cells [36]; however, there are surprisingly few data for carriage rates among nonsmokers and smokers without underlying lung disease. In our study population, there were significantly more smokers among the HIV-infected patients than among controls, and among HIV-infected subjects, smoking appeared to be a risk factor for pneumococcal colonization. This association was not observed for controls. In contrast, Janoff et al. [4] observed a higher carriage rate among smokers than nonsmokers among non-HIV-infected subjects, suggesting the organisms were newly acquired. Both had received pneumococcal vaccine. Other studies suggest such invasive disease is more closely related to persistence of the carrier state [41]. Two of the HIV-infected patients in our study (1 in each group) developed pneumococcal pneumonia during the study period (3 and 6 months after immunization). In 1 patient, the organism (serotype 11) was cultured from blood; the sputum isolate from the other was not available for serotyping. Neither patient had pneumococci previously found in their throats, suggesting the organisms were newly acquired. Both had received 23-valent pneumococcal vaccine.

The effect of immunization on pneumococcal colonization has seldom been studied, and results have been controversial. In military recruits, immunization reduced colonization [42], but results of Papua New Guinea vaccine trials [43] did not suggest a reduction in carriage of vaccine serotypes in the immunized population. In children, both Haemophilus influenzae type b [44, 45] and S. pneumoniae [46] were significantly reduced after immunization with conjugate vaccines. In our HIV-infected patients, vaccination with the 23-valent polysaccharide or a pentavalent protein-conjugate vaccine did not reduce colonization compared with baseline levels; however, we lack comparison data for an unvaccinated group. In addition, the sample size of the present study enabled comparison of the
immunogenicity of the 2 vaccines [7] but lacked the necessary power to detect differences between them (at a significance level of .05) on the effect in colonization.

Children attending day care centers are more likely than children staying at home to be pneumococcal carriers and to carry resistant organisms [12, 47, 48]. Factors in day care settings that favor the development and transmission of resistant organisms include intensive antibiotic use, many children, and frequent close interpersonal contacts [49]. Many of the same factors occur in clinics and facilities for HIV-infected patients. In children, nosocomial transmission of resistant pneumococci has been documented [50].

In our study, by BOX-PCR DNA analysis, 2 pairs of subjects had indistinguishable organisms. This suggests the possibility of transmission of organisms between patients, prevalence of the bacterial clones in the geographic area, or little clonal variation in the serotypes (as shown for serogroup 9) [30, 31]. In our study, resistant organisms were uniformly distributed among all serotypes, including nontypeable isolates. The fact that no resistant serotypes predominated suggests that resistance likely developed secondary to antibiotic pressure and not to spread of a resistant clone. All isolates from HIV-infected subjects were sensitive to chloramphenicol, a drug seldom given to these patients. This supports the concept that, as in other populations [47, 48], previous and frequent exposure to antibiotics is an important factor for the emergence of resistance in HIV-infected subjects [51]. In contrast to our findings, Janoff et al. [4] did not find any penicillin-resistant S. pneumoniae in HIV-infected carriers. However, in that study, antibiotic use within the prior 2 weeks was an exclusion criteria, and perhaps as a consequence, antibiotic use in the population was low (5% in the preceding 6 months).

In HIV-infected adults, prophylaxis with trimethoprim-sulfamethoxazole against Pneumocystis carinii pneumonia has been associated with fewer invasive pneumococcal infections [52]. We found that carriage rate at baseline among HIV-infected subjects with <200 CD4 cells/μL was less than half that of subjects with more CD4 cells, suggesting that trimethoprim-sulfamethoxazole prophylaxis may have a protective effect. However, the carriage rate in the patients with <200 CD4 cells/μL seemed to increase with time. This phenomenon may have been related to seasonal peaks, to progressive immunosuppression, or to the emergence of trimethoprim-sulfamethoxazole-resistant isolates. Because the majority of colonizing isolates from this group were resistant to trimethoprim-sulfamethoxazole, we favor the last hypothesis.

The increased rate of colonization by organisms resistant to penicillin and other antibiotics is clinically relevant. The antibiotic resistance of carriage organisms approximates the resistance patterns of invasive organisms and thus may be useful for monitoring changing patterns of antimicrobial susceptibility in the community [28, 41]. Recent studies have shown that HIV-infected patients are more likely to have invasive disease due to resistant organisms than are non-HIV-infected subjects [15–17]. Antibiotic susceptibility testing should be done routinely in all S. pneumoniae clinical isolates from HIV-infected patients, regardless of their source. Because of the high prevalence of antibiotic resistance in this population, suspected cases of severe pneumococcal infection should be treated with third-generation cephalosporins until antibiotic susceptibility results are available.

Despite concerns about increases in virus load in association with immunization [53–55], pneumococcal vaccination should be given as early as possible after HIV infection is diagnosed [7, 56]. Patients with <200 CD4 cells/μL are at a greater risk for pneumococcal disease [4, 57] and are less likely to have an adequate antibody response to pneumococcal immunization [3, 7]. In these patients, the chronic use of trimethoprim-sulfamethoxazole did not prevent colonization and was a risk factor for the acquisition of trimethoprim-sulfamethoxazole-resistant isolates. HIV-infected adults, like children in day care centers [58], constitute a reservoir of antibiotic-resistant S. pneumoniae from which spread to others in the community might be expected. Immunization with pneumococcal vaccine of persons at risk of exposure to penicillin-resistant pneumococci should be given strong consideration.

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