

THE PREVALENCE OF DRUG-RESISTANT *STREPTOCOCCUS PNEUMONIAE* IN ATLANTA

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Abstract *Background.* *Streptococcus pneumoniae* is a major cause of illness, and the emergence of drug-resistant strains threatens to complicate the management of pneumococcal infections. We conducted a laboratory-based surveillance for drug-resistant *S. pneumoniae* among patients with invasive pneumococcal infections in Atlanta.

Methods. From January through October 1994, pneumococcal isolates from 431 patients with invasive disease in metropolitan Atlanta were serotyped and tested to determine their susceptibility to various antimicrobial agents. Susceptibility to the antimicrobial agents was defined according to guidelines established by the National Committee for Clinical Laboratory Standards.

Results. The annual incidence of invasive pneumococcal infection was 30 cases per 100,000 population. Isolates from 25 percent of the patients were resistant to penicillin (7 percent were highly resistant), and isolates from 26 percent were resistant to trimethoprim-sulfamethoxazole (7 percent highly resistant). Fifteen percent

of the isolates were resistant to erythromycin, 9 percent to cefotaxime (4 percent were highly resistant), and 25 percent to multiple drugs. Drug-resistant pneumococci were found in both children and adults. Children under six years of age were more likely than older children and adults to have isolates resistant to multiple drugs or cefotaxime. Whites were more likely than blacks to have invasive pneumococcal infections caused by drug-resistant organisms. Among white children younger than six years, 41 percent of the *S. pneumoniae* isolates were resistant to penicillin.

Conclusions. Drug-resistant strains of *S. pneumoniae* are common among both children and adults in Atlanta. Although blacks had a higher incidence of invasive pneumococcal infections than whites, whites were more likely to be infected with a drug-resistant isolate. Control of drug-resistant pneumococci will require more judicious use of antimicrobial agents and wider use of the pneumococcal polysaccharide vaccine. (*N Engl J Med* 1995;333:481-6).

S*TREPTOCOCCUS PNEUMONIAE* is a major cause of morbidity and mortality and results in expenditures of over \$4 billion yearly in the United States for the treatment of pneumonia, meningitis, bacteremia, sinusitis, and otitis media.¹⁻³ The emergence of drug-resistant *S. pneumoniae* will make these common infections more difficult to treat.⁴⁻⁶ Most reports regarding drug-resistant pneumococcus in the United States have focused on infections in children, in which the spread of drug-resistant organisms has been linked to day-care centers and the indiscriminate use of antibiotics.⁷⁻¹¹ To characterize the epidemiology of drug-resistant *S. pneumoniae*, we conducted population-based surveillance for invasive pneumococcal infections in metropolitan Atlanta. We found a high prevalence of drug-resistant *S. pneumoniae* in both children and adults.

METHODS

In November 1988, Emory University School of Medicine and the Centers for Disease Control and Prevention (CDC) established a laboratory-based program of surveillance for bacterial pathogens in conjunction with the Georgia Department of Human Resources.¹² Surveillance for invasive pneumococcal disease was performed prospectively from January 1 to December 31, 1994. Pneumococcal isolates from normally sterile sites were collected from the microbiology laboratories of 32 hospitals (including all 28 acute care hospitals) and 1 major reference laboratory in the eight-county metropolitan Atlanta area. The population of the surveillance area is 2.34 million per-

sons (68 percent white, 29 percent black, and 3 percent other racial or ethnic groups). Laboratories submitted pneumococcal isolates obtained from normally sterile sites and provided demographic data and limited clinical information on the patients from whom isolates were obtained. Laboratory audits were performed at least every six months to evaluate reporting accuracy and identify cases not reported by surveillance. Patients were excluded from the analysis if they resided outside the surveillance area (n=65), their place of residence was unknown (n=8), or the source of their isolate was unknown (n=3). Duplicate isolates from the same patient were excluded if less than 30 days separated each episode of pneumococcal infection. Antimicrobial-susceptibility testing was performed on all eligible isolates collected from January 1 through October 31, 1994.

S. pneumoniae isolates were sent to the CDC on blood-agar slant cultures and confirmed as pneumococci on the basis of their susceptibility to ethylhydrocupreine (optochin) and bile solubility.¹³ Isolates were serotyped with the quellung reaction with type-specific antiserum prepared at the CDC.¹³

Antimicrobial-susceptibility testing was performed by the broth-dilution method.¹³ To determine the minimal inhibitory concentration (MIC) of each isolate, customized panels of antimicrobial agents were prepared by Radiometer America (Sensititre, Westlake, Ohio). The following concentrations of antimicrobial agents (expressed in micrograms per milliliter) were prepared in lyophilized panels: penicillin, 0.015 to 8; chloramphenicol, 1 to 32; trimethoprim and sulfamethoxazole, 0.06 to 8 and 1.2 to 152, respectively; erythromycin, 0.06 to 8; tetracycline, 0.25 to 32; imipenem, 0.06 to 32; vancomycin, 0.5 to 8; ofloxacin, 0.03 to 4; cefotaxime, 0.015 to 8; cefaclor, 0.25 to 16; clarithromycin, 0.06 to 8; and rifampin, 0.12 to 4. Cultures for preparing the inoculum were grown for 18 hours in an incubator with 5 percent carbon dioxide on plates containing tryptic soy agar with 5 percent sheep's blood (Becton Dickinson Microbiology Systems, Cockeysville, Md.). A suspension of cells equal to that of a 0.5 McFarland turbidity standard was prepared in Mueller-Hinton broth (Becton Dickinson Microbiology Systems) with an A-just turbidimeter (Abbott Laboratories, North Chicago, Ill.) according to the recommendations of the National Committee for Clinical Laboratory Standards, and 10 μ l of this suspension was added to 10 ml of cation-adjusted Mueller-Hinton broth supplemented with 5 percent lysed horse blood. The MIC panels were inoculated with the Autoinoculator V2010 (Sensititre). We read growth visually by holding the MIC panel in front of an incandescent lamp. The MIC was defined as the

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lowest concentration of drug that inhibited growth. To ensure consistency among test results, we tested MICs of a strain of *S. pneumoniae* with known drug-susceptibility patterns each day that surveillance isolates were tested.

The susceptibility standards for each drug were defined according to 1994 National Committee for Clinical Laboratory Standards break points (clear guidelines do not exist for cefaclor; therefore, the break point proposed in 1993 by the National Committee for Clinical Laboratory Standards was used) (Table 1).^{14,15} For the purposes of this report, the category of resistant isolates includes all those with decreased susceptibility (both intermediate- and high-level resistance). The National Committee for Clinical Laboratory Standards has recently redefined this terminology so that "decreased susceptibility" comprises two categories: intermediate (formerly called low-level resistance) and resistant (formerly called high-level resistance).¹⁵ Multidrug resistance was defined as an intermediate level of susceptibility or resistance to two or more of the following antimicrobial drugs or drug classes: β -lactam antibiotics and carbapenems (including penicillin, cephalosporins, and imipenem), macrolides, trimethoprim-sulfamethoxazole, tetracycline, ofloxacin, and chloramphenicol.

Ninety-five percent confidence intervals for risk ratios were calculated according to the method of Greenland and Robins¹⁶; P values were calculated by Fisher's two-tailed exact test. Calculations were performed with the Epi Info statistical program (version 6.0a; CDC, Atlanta).

RESULTS

A total of 527 cases of invasive pneumococcal disease were identified among residents of metropolitan Atlanta between January 1 and October 31, 1994; 431 cases had invasive pneumococcal isolates available for our analysis (82 percent of all invasive pneumococcal infections occurring during the study period). In their mean age, race or ethnic group, county of residence, and outcome, patients for whom isolates were available were similar to patients for whom isolates were not available. The patients ranged in age from 2 days to 94 years (mean, 35.3 years); 24 percent of the isolates were from children less than 2 years of age, 9 percent

from children 2 to 5 years, 2 percent from children 6 to 17 years, and 64 percent from adults 18 years and older. Fifty-four percent of the case patients were male, and 46 percent were female. Fifty-five percent were black, 44 percent white, and 1 percent Asian or another racial or ethnic group. Of the 431 isolates, 415 (96 percent) were from blood, 10 (2 percent) from cerebrospinal fluid, 3 (0.7 percent) from joint fluid, and 1 (0.2 percent) each from bone (mastoid), peritoneal fluid, and pleural fluid.

On the basis of 1990 census data and cases identified by audit from January through December 31, 1994 (n = 712), the overall incidence of invasive pneumococcal infection in 1994 was 30 cases per 100,000 population; the incidence was 18 cases per 100,000 population among whites and 58 cases per 100,000 population among blacks.¹⁷ Using the proportions of infections with penicillin-resistant organisms among whites and blacks from January through October 1994, we determined that the annualized incidence of infections with penicillin-resistant isolates was 6 per 100,000 among whites and 11 per 100,000 among blacks.¹⁷

Isolates from 25 percent of the patients were resistant to penicillin; 7 percent had high-level resistance (Table 1). Nine percent of the isolates were resistant to cefotaxime; 4 percent had high-level resistance. More than 10 percent of the isolates were resistant to macrolides, trimethoprim-sulfamethoxazole, and cefaclor; all strains were susceptible to vancomycin and rifampin. All isolates resistant to cefotaxime, chloramphenicol, or imipenem were also resistant to penicillin; resistance to penicillin was common among isolates resistant to cefaclor (98 percent), tetracycline (77 percent), trimethoprim-sulfamethoxazole (75 percent), and erythromycin (68 percent). Of the 109 isolates resistant to penicillin, 75 percent were resistant to trimethoprim-sulfamethoxazole, 41 percent to erythromycin, and 34 percent to cefotaxime (Table 2). Thirty-seven isolates (9 percent) were resistant to both penicillin and cefotaxime; many of these isolates were also resistant to trimethoprim-sulfamethoxazole, erythromycin, tetracycline, or chloramphenicol (Table 2). Fifteen isolates (3 percent) had high-level resistance to both penicillin and cefotaxime; all were also resistant to trimethoprim-sulfamethoxazole. Isolates from 106 patients (25 percent) were resistant to multiple drugs, including 46 (11 percent) that were resistant to three or more antimicrobial drugs or drug classes.

Pneumococcal isolates from both children and adults exhibited high levels of resistance to antimicrobial drugs (Fig. 1). For the comparison of strains from children under six years of age with those from all other patients in the study (≥ 6 years of age) there were no significant differences in the proportions of isolates resistant to penicillin (27 percent and 24 percent, respectively; risk ratio, 1.12; 95 percent confidence interval, 0.80 to 1.57) or highly resistant to both penicillin and cefotaxime (6 percent and 2 percent; risk ratio, 2.27; 95 percent confidence interval, 0.84 to 6.14) (Table 3). However, the young children were more likely than old-

Table 1. Proportions of Pneumococcal Isolates Resistant to Specific Antimicrobial Drugs from 431 Patients in Metropolitan Atlanta, January through October 1994.*

DRUG	LEVEL OF RESISTANCE	MIC <i>μg/ml</i>	No. (%) RESISTANT	TOTAL No. (%) RESISTANT
Penicillin	Intermediate	0.12–1.2	77 (18)	109 (25)
	High	≥ 2	32 (7)	
Cefotaxime	Intermediate	1	20 (5)	37 (9)
	High	≥ 2	17 (4)	
Cefaclor	Intermediate	8–16	15 (3)	61 (14)
	High	> 16	46 (11)	
Erythromycin	Intermediate	1–2	14 (3)	66 (15)
	High	≥ 4	52 (12)	
Trimethoprim-sulfamethoxazole	Intermediate	1–2	79 (18)	110 (26)
	High	≥ 4	31 (7)	
Chloramphenicol	High	≥ 8	13 (3)	13 (3)
Clarithromycin	Intermediate	1	5 (1)	63 (15)
	High	≥ 2	58 (13)	
Ofloxacin	Intermediate	4	4 (1)	4 (1)
	High	≥ 8	0	
Tetracycline	Intermediate	4	1 (0.2)	34 (8)
	High	≥ 8	33 (8)	
Imipenem	Intermediate	0.25–0.5	17 (4)	25 (6)
	High	≥ 1	8 (2)	

*No isolates were resistant to rifampin or vancomycin.

Table 2. Proportions of Pneumococcal Isolates Resistant to Penicillin and Cefotaxime That Were Also Resistant to Other Antimicrobial Drugs in Metropolitan Atlanta, January through October 1994.

DRUG	PENICILLIN-RESISTANT	CEFOTAXIME-RESISTANT
	no. (%)	
Penicillin	—	37 (100)
Trimethoprim-sulfamethoxazole	82 (75)	35 (95)
Cefaclor	59 (54)	25 (68)
Cefotaxime	37 (34)	—
Erythromycin	45 (41)	18 (49)
Tetracycline	26 (24)	14 (38)
Imipenem	25 (23)	24 (65)
Chloramphenicol	13 (12)	9 (24)
Ofloxacin	1 (1)	0
Multiple drugs	86 (79)	35 (95)
Total no. of resistant isolates	109	37

er patients to have isolates resistant to cefotaxime (12 percent vs. 7 percent; risk ratio, 1.88; 95 percent confidence interval, 1.02 to 3.47) or to multiple drugs (33 percent vs. 20 percent; risk ratio, 1.61; 95 percent confidence interval, 1.16 to 2.24) (Table 3).

A much higher proportion of whites than blacks was infected with penicillin-resistant isolates (32 percent vs. 19 percent; risk ratio, 1.66; 95 percent confidence interval, 1.18 to 2.32) and multidrug-resistant isolates (30 percent vs. 20 percent; risk ratio, 1.54; 95 percent confidence interval, 1.10 to 2.16). As compared with black children under six years of age, white children under six years of age had higher proportions of isolates resistant to penicillin (41 percent vs. 20 percent; risk ratio, 2.09; 95 percent confidence interval, 1.21 to 3.60), cefotaxime (22 percent vs. 7 percent; risk ratio, 3.26; 95 percent confidence interval, 1.28 to 8.26), or multiple drugs (47 percent vs. 25 percent; risk ratio, 1.86; 95 percent confidence interval, 1.16 to 2.96) (Table 3).

Among the eight counties that were monitored, there were no statistically significant differences in the proportions of drug-resistant isolates. As compared with the two urban counties (Fulton and DeKalb) that make up the city of Atlanta, the six suburban counties were more likely to have residents infected with penicillin-resistant isolates (34 percent vs. 20 percent; risk ratio, 1.69; 95 percent confidence interval, 1.22 to 2.32) or multidrug-resistant isolates (33 percent vs. 20 percent; risk ratio, 1.65; 95 percent confidence interval, 1.19 to 2.29).

The proportion of infections with penicillin-resistant organisms was

greater among suburban blacks than among urban blacks (31 percent vs. 15 percent; risk ratio, 1.75; 95 percent confidence interval, 0.98 to 3.13). Among whites, the difference in the proportion of penicillin-resistant strains isolated from suburban and urban residents was less pronounced (36 percent vs. 26 percent; risk ratio, 1.33; 95 percent confidence interval, 0.84 to 2.11), as was the difference in penicillin resistance among white and black suburban residents (36 percent vs. 30 percent; risk ratio, 1.17; 95 percent confidence interval, 0.67 to 2.03).

Six serotypes — 14, 6B, 9V, 23F, 19A, and 6A — accounted for over 85 percent of the isolates resistant to penicillin, cefotaxime, or multiple drugs (Table 4). As compared with all other serotypes, 23F was significantly associated with cefotaxime resistance (41 percent vs. 6 percent; risk ratio, 7.71; 95 percent confidence interval, 4.42 to 13.48), as well as high-level resistance to both penicillin and cefotaxime (37 percent vs. 1 percent; risk ratio, 73.54; 95 percent confidence interval, 17.28 to 312.91). Among the 15 isolates with high-level resistance to penicillin and cefotaxime, 13 were serotype 23F, 1 was serotype 6A, and 1 was serotype 6B.

DISCUSSION

Our data indicate a high prevalence of drug-resistant strains of *S. pneumoniae* in metropolitan Atlanta. In response to previous reports of drug-resistant strains of pneumococci in children, recommendations are being formulated for empirical therapy for life-threatening pneumococcal infections in children.^{6-11,18-27} In Atlanta, children under six years of age were more likely than older children and adults to be infected with cefotaxime-resistant or multidrug-resistant isolates; however, we found a disturbingly high incidence of drug-resistant pneumococcal infections among adults. Our data suggest that recommendations for empirical therapy

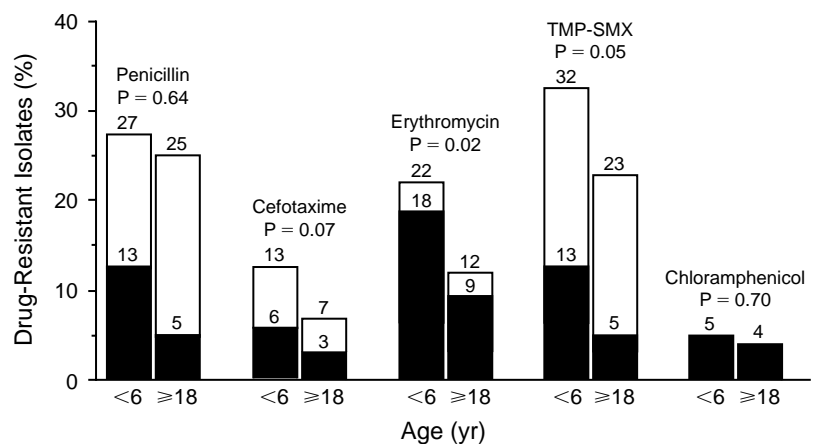


Figure 1. Proportion of Pneumococcal Strains Resistant to Common Antimicrobial Drugs That Were Isolated from Children and Adults in Metropolitan Atlanta, January through October 1994.

The level of resistance was considered to be high (solid bars) or intermediate (open bars), as explained in the Methods section. Nine patients who were 6 to 17 years of age were excluded from the analysis. TMP-SMX denotes trimethoprim-sulfamethoxazole.

are needed for pneumococcal infections in adults as well as children, particularly in communities in which the prevalence of drug-resistant *S. pneumoniae* is high.

Increasing numbers of reports of drug-resistant *S. pneumoniae* appeared from outside the United States during the 1970s; however, reports of infections with strains with high-level resistance to penicillin in the United States have only emerged more recently.^{18,28,29} From 1979 to 1987, 0.02 percent of isolates identified in a nationwide program of surveillance for pneumococcal infection had high-level resistance to penicillin; by 1992, the proportion of such isolates had risen to 1.3 percent.^{30,31}

Recent studies of adults and children in a variety of communities have found proportions of penicillin-resistant invasive pneumococci ranging from 2 to 17 percent.^{11,19,21,30-35} The geographic variation in the prevalence of drug-resistant strains of pneumococci in the United States highlights the importance of community-based monitoring of pneumococcal susceptibility to antimicrobial agents to guide therapy. In addition, the increased prevalence of drug-resistant *S. pneumoniae* emphasizes the critical need for preventive strategies in populations at risk for serious pneumococcal infections.

Frequent and prophylactic use of antimicrobial drugs has been associated with a risk of drug-resistant pneumococcal infections, probably as a result of selective pressure.^{9,11,23-26,36-39} Despite a greater incidence of invasive pneumococcal infections in blacks, whites (particularly those under six years of age) in our study were at increased risk for drug-resistant *S. pneumoniae* infections. Similar associations have been reported in previous studies.^{10,34} Suburban residence was also associ-

Table 4. Serotypes of Drug-Resistant Pneumococcal Isolates in Metropolitan Atlanta, January through October 1994.*

SEROTYPE†	ISOLATES	PENICILLIN-RESISTANT	CEFOTAXIME-RESISTANT	HIGH-LEVEL RESISTANCE TO PENICILLIN AND CEFOTAXIME	MULTIDRUG-RESISTANT
14	93 (22)	15 (14)	2 (5)	0	26 (25)
6B	44 (10)	23 (21)	14 (38)	1 (7)	24 (23)
9V	41 (10)	11 (10)	3 (8)	0	7 (7)
4	37 (9)	0	0	0	0
23F	35 (8)	16 (15)	15 (41)	13 (87)	17 (16)
19A	25 (6)	17 (16)	0	0	8 (8)
6A	24 (6)	15 (14)	2 (5)	1 (7)	15 (14)
19F	24 (6)	5 (5)	0	0	5 (5)
Other‡	108 (25)	7 (6)	1 (3)	0	4 (4)
Total	431	109	37	15	106

*Because of rounding, not all columns total 100 percent.

†The serotypes listed are all included in the 23-valent vaccine except for 6A, which cross-reacts with vaccine serotype 6B.

‡Each serotype in this category made up less than 4 percent of the total number of isolates.

ated with an increased risk of infection with a drug-resistant organism. White race, suburban residence, or both may be surrogates for socioeconomic status and access to medical care. Hence, this association may be due to more frequent use of antimicrobial drugs among a more affluent population in metropolitan Atlanta.^{11,34,36,40} Recent studies have suggested that excessive and inappropriate use of antimicrobial drugs is widespread, particularly among white patients.^{36,40} A critical component for the control of drug-resistant *S. pneumoniae* will be community-wide educational programs for clinicians and the public on the importance of appropriate antibiotic use.

The optimal therapy for infections with drug-resistant pneumococci is not well defined. Studies have suggested that cephalosporins or high-dose penicillin may be effective in patients with nonmeningeal bacteremic infections if the MIC of penicillin is 2 µg per milliliter or less.^{4,20,39} Recent reports have described the failure of extended-spectrum cephalosporins, chloramphenicol, and vancomycin in pneumococcal meningitis due to organisms with intermediate-level or high-level resistance to penicillin or cephalosporins.^{5,41} Although these reports suggest that the emergence of drug-resistant pneumococcus will make treatment failures increasingly common, controlled studies are needed to evaluate the impact of drug-resistant *S. pneumoniae* on the clinical outcome of all pneumococcal infections. The efficacy of combination therapy with an extended-spectrum cephalosporin and vancomycin or rifampin for meningitis caused by a pneumococcus resistant to extended-spectrum cephalosporins has not yet been definitively demonstrated.⁴² Additional data identifying optimal alternatives

Table 3. Drug-Resistant Pneumococcal Strains Isolated from Patients in Metropolitan Atlanta, January through October 1994, According to Age and Race.

RACE AND AGE GROUP*	NO. OF PATIENTS	PENICILLIN-RESISTANT	CEFOTAXIME-RESISTANT	HIGH-LEVEL RESISTANCE TO PENICILLIN AND CEFOTAXIME	MULTIDRUG-RESISTANT
All patients	430	108 (25)	37 (9)	15 (3)	105 (24)†
<6 yr	144	39 (27)	18 (12)‡	8 (6)	47 (33)‡
≥6 yr	286	69 (24)	19 (7)	7 (2)	58 (20)
White	183	59 (32)§	19 (10)	8 (4)	55 (30)§
<6 yr	49	20 (41)¶	11 (22)¶	5 (10)	23 (47)¶
≥6 yr	134	39 (29)	8 (6)	3 (2)	32 (24)
Black	231	45 (19)	16 (7)	6 (3)	46 (20)
<6 yr	87	17 (20)	6 (7)	2 (2)	22 (25)
≥6 yr	144	28 (19)	10 (7)	4 (3)	24 (17)

*Information on race was available for 416 patients; 2 Asian patients were not included in the analysis because of the small sample size.

†Data were missing for one patient.

‡P<0.05 for the comparison with patients ≥6 years of age.

§P<0.05 for the comparison with black patients.

¶P<0.05 for the comparison with black patients <6 years of age.

to β -lactam therapy for life-threatening infections (e.g., meningitis) due to drug-resistant *S. pneumoniae* are clearly needed. In the absence of such information, initial use of both an extended-spectrum cephalosporin and vancomycin should be strongly considered for children and adults with suspected pneumococcal meningitis until the results of susceptibility testing are available. For the treatment of less serious infections, the addition of vancomycin should not be necessary in most cases.

The vast majority of invasive pneumococcal isolates resistant to penicillin, cefotaxime, and multiple drugs belonged to one of six serotypes. These six serotypes have been associated with invasive drug-resistant *S. pneumoniae* infections in children and adults in previous studies.^{31,43,44} All are included in the currently available 23-valent pneumococcal polysaccharide vaccine (or, in the case of 6A, stimulate the production of cross-protective antibodies). Although the efficacy of pneumococcal vaccine has been estimated to be 60 to 70 percent in most targeted populations, it is underused.^{45,46} Children less than two years of age do not consistently produce protective antibodies to capsular-polysaccharide vaccines; however, efforts are under way to develop conjugate pneumococcal vaccines for this age group.⁴⁷ Several proposed conjugate-vaccine formulations include serotypes 6B, 9V, 14, 19F, and 23F.⁴⁷

With the continuing spread of drug-resistant strains of pneumococci, treatment options for invasive disease will become more limited, and prevention measures will become critical. This study emphasizes the importance of antimicrobial-susceptibility testing of all invasive pneumococcal isolates from both children and adults in the United States, as well as the crucial need for community-based programs of surveillance for drug-resistant pneumococcus to aid clinicians in their choice of therapy for pneumococcal infections. The prevention of infections with invasive drug-resistant pneumococcus will require strategies to encourage judicious antibiotic use and optimize immunization with the 23-valent pneumococcal vaccine in targeted populations. Pneumococcal conjugate vaccines hold promise for the prevention of invasive disease in children under two years of age and should be evaluated quickly. With the emergence of drug-resistant *S. pneumoniae*, recommendations for the treatment and prevention of pneumococcal infections must be addressed by health care and public health agencies. Our data suggest an urgent need for consensus guidelines for the prevention and treatment of drug-resistant pneumococcal infections.

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