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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

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A total of 1,527 clinically significant outpatient isolates of *Streptococcus pneumoniae* were prospectively collected in 30 different U.S. medical centers between November 1994 and April 1995. Overall, 23.6% of strains were not susceptible to penicillin, with 14.1% intermediate and 9.5% high-level resistant. The frequencies of recovery of intermediate and high-level resistant strains varied considerably between different medical centers and in different geographic areas. In general, intermediate and high-level penicillin resistance was most common with isolates of *S. pneumoniae* recovered from pediatric patients. The in vitro activities of 22 other antimicrobial agents were assessed against this collection of isolates. Ampicillin was consistently 1 twofold dilution less active than penicillin. Amoxicillin and amoxicillin-clavulanate were essentially equivalent to penicillin in activity. The rank order of activity for cephalosporins was cefotaxime = ceftriaxone ≥ cefpodoxime ≥ cefuroxime > cefprozil ≥ cefixime > cefaclor = loracarbef > cefadroxil = cephalexin. The National Committee for Clinical Laboratory Standards [*Performance Standards for Antimicrobial Susceptibility Testing*, *Sixth Information Supplement* (*M100-S6*), 1995] has established MIC breakpoints for resistance (i.e., ≥2 μg/ml) with three cephalosporins versus *S. pneumoniae*, namely, cefotaxime, ceftriaxone, and cefuroxime. The overall percentages of strains resistant to these three antimicrobial agents were 3, 5, and 12, respectively. The overall frequency of resistance was 10% with all three macrolides examined in this study, clarithromycin, erythromycin, and azithromycin. The overall percentages of chloramphenicol, tetracycline, and trimethoprim-sulfamethoxazole resistance were 4.3, 7.5, and 18, respectively. The resistance percentages among the cephalosporins, macrolides, chloramphenicol, tetracycline, and trimethoprim-sulfamethoxazole were consistently higher among penicillin-intermediate strains than among susceptible isolates and even higher still among organisms expressing high-level penicillin resistance. Multiply resistant strains represented 9.1% of the organisms examined in this study. Finally, rifampin resistance was uncommon (i.e., 0.5%), and vancomycin resistance was not detected. The quinopristin-dalfopristin combination was consistently active at concentrations of 0.25 to 4 μg/ml, but rates of resistance could not be determined in the absence of established interpretive criteria for MIC results.

Prior to the early 1990s, penicillin resistance remained uncommon among clinical isolates of *Streptococcus pneumoniae* in the United States despite the emergence of this problem in many other parts of the world (1, 10). In an ongoing national surveillance program conducted by the Centers for Disease Control through the decade of the 1980s, strains of *S. pneumoniae* that were not penicillin susceptible were recovered infrequently, i.e., 3 to 6% (23). Furthermore, among those strains found not to be susceptible to penicillin, nearly all were penicillin intermediate (Pen^i) (i.e., penicillin MICs = 0.1 to 1.0 μg/ml). High-level resistant strains (Pen^r) (i.e., penicillin MICs of ≥2.0 μg/ml) were extremely uncommon. These findings were corroborated by one large independent national surveillance study that characterized 487 isolates from 15 U.S. medical centers in 1987 to 1988 (9). In this study, the percentages of Pen^i and Pen^r strains were found to be 3.8 and 0.2, respectively.

A major increase in the prevalence of penicillin resistance with the pneumococcus evidently took place some time during the early 1990s in the United States, because a national surveillance study performed by Thornsberry and colleagues which characterized 524 isolates from 17 centers during 1991 to 1992 now demonstrated an aggregate percentage of intermediate and high-level resistance of 17.8%, with 15.2% Pen^i and 2.6% Pen^r (24). One year later during 1992 to 1993, Barry and coworkers observed even higher rates of penicillin resistance in a second U.S. national surveillance study (2). Among 799 isolates from 19 U.S. medical centers, the prevalence of Pen^i was 14.9%, and the prevalence of Pen^r was 7.3%.

The mechanism of penicillin resistance is alteration of high-molecular-weight penicillin-binding proteins (PBPs) (11–13). These same PBPs are also important in manifesting the activity of other β-lactams such as the β-lactamase inhibitor combinations, cephalosporins, and carbapenems. As a result, the activity of all of these agents is diminished to at least some extent against pneumococci that are not susceptible to penicillin (2, 3, 6, 9, 12, 22). In general, only cephalosporins with high intrinsic activity against penicillin-susceptible strains (Pen^s) of *S. pneumoniae* (i.e., cefotaxime, ceftriaxone, cefpodoxime, cefuroxime, and perhaps cefprozil) retain sufficient activity against Pen^i strains to be considered of value in treating infections due to such organisms (6, 10). Only cefotaxime and ceftriaxone are thought to be of utility in managing selected infections due to typical pen^r isolates (6, 10). Of great concern are recent reports of clinical isolates of Pen^i *S. pneumoniae* with further alter-

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ations in PBPs that express high-level resistance against cefotaxime and ceftriaxone (4, 7, 20).

In addition to the emergence of β-lactam resistance, isolates of *S. pneumoniae* which are resistant to the macrolides, tetracycline, chloramphenicol, and trimethoprim-sulfamethoxazole (TMP-SMX) either alone or in some combination, are now also being recovered increasingly more often from human clinical material in the United States (2, 10). As was the case with β-lactam-resistant pneumococci, multiresistant strains had been recognized as a problem in other parts of the world prior to their emergence in the United States (1, 8, 10).

The intent of the current multicenter national surveillance study was to clearly define the prevalence of antimicrobial resistance among clinical isolates of *S. pneumoniae* in the United States during the winter of 1994 to 1995. Sampling was performed prospectively in such a way as to provide large numbers of community-acquired isolates representative of different geographic areas, different patient populations, and different infectious disease conditions.

MATERIALS AND METHODS

A total of 1,527 isolates of *S. pneumoniae* were collected from 30 different U.S. medical centers between 1 November 1994 and 31 April 1995 (Table 1). In all cases, isolates characterized in this study were recovered from consecutive unique nonhospitalized patients. With the exception of lower respiratory tract specimens, all isolates were obtained from specimens representative of normally sterile body sites (see Table 3). When recovered from lower respiratory tract specimens, only isolates of *S. pneumoniae* judged to be of at least probable clinical significance were included. In contributing study centers, isolates were subcultured onto 5% sheep blood agar plates and incubated overnight at 35 to 37°C in 5 to 7% CO_2. A large amount of colony growth was collected on a rayon swab and immediately immersed in a specially devised, plastic-cap transport tube containing 12 ml of semisolid Aimes transport medium with charcoal (Difco Laboratories, Detroit, Mich.). Transport tubes were then shipped overnight to the coordinating study center, the University of Massachusetts Medical Center, where all additional analyses were performed. The recovery rate from this transport system was 100%.

Isolates were frozen at −70°C in the coordinating study center until further characterization. Following two subcultures, the identity of isolates was confirmed as *S. pneumoniae* by conventional tests and criteria. MICs were determined in Mueller-Hinton broth supplemented with 3% lysed horse blood by the broth microdilution method recommended by the National Committee for Clinical Laboratory Standards (NCCLS) (16, 17). Microdilution trays (final volume of 100 μl per well) were inoculated with ca. 5×10^5 CFU/ml (final concentration) of test organism and incubated for 22 to 24 h at 35°C in ambient air prior to determining MICs. The following 23 antimicrobial agents, obtained as laboratory-grade powders from their respective manufacturers, were tested: penicillin, ampicillin, amoxicillin, amoxicillin-clavulanate (2:1), cefotaxime, ceftriaxone, quinopristin-dalfopristin (30:70), cephalexin, cefadroxil, cefaclor, loracarbef, cefprozil, cefuroxime, cefixime, cefpodoxime, erythromycin, azithromycin, clarithromycin, TMP-SMX (1:19), chloramphenicol, tetracycline, rifampin, and vancomycin. Twelve concentrations of each agent were tested such that off-scale results were obtained only infrequently. *S. pneumoniae* ATCC 49619 and *Haemophilus influenzae* ATCC 49247, ATCC 49766, and ATCC 10211 were used as controls.

Calculations of the percentages of isolates resistant to specific antimicrobial agents were restricted to compounds for which the NCCLS has established MIC interpretive criteria defining the resistant category for *S. pneumoniae* (17). These compounds and criteria were as follows: amoxicillin, amoxicillin-clavulanate, cefotaxime, ceftriaxone, cefuroxime, azithromycin, and vancomycin, all ≥2 μg/ml; clarithromycin and erythromycin, ≥1 μg/ml; chloramphenicol and tetracycline, ≥8 μg/ml; and rifampin and TMP-SMX, ≥4 μg/ml. The NCCLS penicillin breakpoints of 0.1 to 1 μg/ml (intermediate category) and ≥2 μg/ml (resistant category) were also employed.

RESULTS

A total of 1,527 isolates of *S. pneumoniae* were characterized in this study (Table 1). Among these isolates, 216 (14.1%) were Pen^i and 145 (9.5%) were Pen^r. The percentage of strains not susceptible to penicillin, i.e., Pen^i plus Pen^r, varied considerably among contributing study centers from a low of 2.1 at Temple University Medical Center in Philadelphia, Pa., to a high of 52.9 at Mt. Sinai Hospital in Miami, Fla. In three centers, the percentages of Pen^i plus Pen^r were ≤10, eight centers had percentages of 11 to 20, nine centers had percentages of 21 to 30, six centers had percentages of 31 to 40, and the remaining four centers had percentages of 41 to 53. Percentages of Pen^i varied between 2.1 and 29.6; Pen^r percentages ranged from 0 to 23.5. In general, the highest percentages of Pen^r were observed in centers with the highest percentages of Pen^i.

Six pediatric hospitals were included in this survey. Pen^i plus Pen^r strains accounted for 30.9% of isolates in these institutions compared with 21.7% in the remaining 24 primarily adult hospitals ($P < 0.005$). This is consistent with the values shown in Tables 2 and 3 where rates of penicillin resistance were sorted by patient age and specimen type. The highest rates of resistance were observed in isolates from patients of ≤5 years of age and from specimens representative of predominantly childhood diseases (i.e., middle ear fluid and sinus aspirates).

Results obtained with 22 other antimicrobial agents are listed in Table 4. Ampicillin appeared to be 1 twofold dilution less active than penicillin for isolates of pneumococci irrespective of penicillin susceptibility category. Amoxicillin and amoxicillin-clavulanate were essentially identical in activity and roughly equivalent to penicillin. Of the cephalosporins tested and compared solely on the basis of MIC values, there emerged a clear rank order of in vitro activity: cefotaxime = ceftriaxone ≥ cefpodoxime ≥ cefuroxime > cefprozil ≥ cefixime > cefaclor = loracarbef > cefadroxil = cephalexin.

By comparing the geometric-mean MICs obtained with a given cephalosporin for Pen^s strains of pneumococci versus the geometric-mean MICs obtained with the same antimicrobial agent for Pen^i and Pen^r strains, the relative influences of the PBP alterations responsible for the two levels of penicillin resistance on cephalosporin activity could be compared (Table 4). The magnitude of increase of cephalosporin MICs as organisms went from Pen^s to Pen^i and from Pen^i to Pen^r varied between 6- and 22-fold with individual antimicrobial agents.

Among the cephalosporins, resistance percentages were calculated only for cefotaxime, ceftriaxone, and cefuroxime, as these are the only agents for which the NCCLS has established interpretive criteria for resistance versus *S. pneumoniae* (17). Overall, 3, 5, and 12% of pneumococcal isolates were resistant to these three antimicrobial agents, respectively. The percentages of resistance among Pen^s, Pen^i, and Pen^r isolates were, respectively, 0, 1, and 32% for cefotaxime; 0, 2, and 50% for ceftriaxone; and 0.4, 36, and 100% for cefuroxime.

Rifampin activity was comparable among Pen^s, Pen^i, and Pen^r strains, with a total of 7 (0.5%) strains resistant to rifampin (i.e., MICs of ≥4 μg/ml) (Table 4). Similarly, no difference in activity was noted with vancomycin and quinopristin-dalfopristin among the three groups of pneumococci, with vancomycin being ca. fourfold more active than the combination. No vancomycin resistance was observed. The frequency of resistance with quinopristin-dalfopristin could not be calculated because of the absence of accepted MIC breakpoints for pneumococci.

The rank order of relative in vitro activities of the three macrolides examined in this study for the pneumococcus was clarithromycin ≥ erythromycin ≥ azithromycin (Table 4) when MIC_{50}s (MICs at which 50% of the isolates are inhibited), MIC_{90}s, and geometric-mean MICs were compared. In terms of overall prevalence of resistance, however, the macrolides appeared equivalent, with 10% of all study isolates found to be resistant to all three agents. Similar observations were made when rates of macrolide resistance were compared with strains in the three penicillin resistance categories. The resistance percentages with all three macrolides were 4 with Pen^s strains, 19 to 20% with Pen^i isolates, and 49% with Pen^r isolates. There

TABLE 1. Recovery of penicillin-resistant *S. pneumoniae* from 30 U.S. medical centers during 1994 and 1995

Medical center	Location	Total no. of isolates	No. (%) of isolates that were penicillin:		
			Susceptible	Intermediate	Resistant
Children's Hospital	Boston, Mass.	36	26 (72.2)	2 (5.6)	8 (22.2)
University of Massachusetts Medical Center	Worcester, Mass.	30	25 (83.3)	4 (13.3)	1 (3.3)
Hartford Hospital	Hartford, Conn.	61	55 (90.2)	3 (4.9)	3 (4.9)
SUNY Medical Center	Syracuse, N.Y.	23	21 (91.3)	2 (8.7)	0 (0.0)
Strong Memorial Hospital	Rochester, N.Y.	58	52 (89.7)	3 (5.2)	3 (5.2)
Columbia-Presbyterian Hospital	New York, N.Y.	64	56 (87.5)	4 (6.3)	4 (6.3)
Temple University Medical Center	Philadelphia, Pa.	47	46 (97.9)	1 (2.1)	0 (0.0)
Geisinger Medical Center	Danville, Pa.	57	45 (78.9)	6 (10.5)	6 (10.5)
National Children's Hospital	Washington, D.C.	60	46 (76.7)	10 (16.5)	4 (6.7)
University of North Carolina Medical Center	Chapel Hill, N.C.	60	40 (66.7)	14 (23.3)	6 (10.0)
DeKalb General Hospital	Decateur, Ga.	61	40 (65.6)	9 (14.8)	12 (19.7)
Mt. Sinai Hospital	Miami, Fla.	17	8 (47.1)	5 (29.4)	4 (23.5)
University of South Alabama Medical Center	Mobile, Ala.	68	54 (79.4)	9 (13.2)	5 (7.4)
Cleveland Clinic	Cleveland, Ohio	42	34 (81.0)	2 (4.8)	6 (14.3)
Henry Ford Hospital	Detroit, Mich.	63	51 (81.0)	11 (17.5)	1 (1.6)
Methodist Hospital	Indianapolis, Ind.	63	50 (79.4)	11 (17.5)	2 (3.2)
Rush Presbyterian Medical Center	Chicago, Ill.	41	26 (63.4)	9 (22.0)	6 (14.6)
Evanston Hospital	Evanston, Ill.	49	42 (85.7)	5 (10.2)	2 (4.1)
Children's Hospital	Milwaukee, Wis.	65	43 (66.2)	13 (20.0)	9 (13.8)
Mayo Clinic	Rochester, Minn.	35	24 (68.6)	7 (20.0)	4 (11.4)
Jewish Hospital	St. Louis, Mo.	56	42 (75.0)	11 (19.6)	3 (5.4)
University of Texas SW Medical Center	Dallas, Tex.	58	45 (77.6)	5 (8.6)	8 (13.8)
Texas Children's Hospital	Houston, Tex.	63	47 (74.6)	6 (9.5)	10 (15.9)
Denver General Hospital	Denver, Colo.	62	53 (85.5)	7 (11.3)	2 (3.2)
Primary Children's Hospital	Salt Lake City, Utah	62	37 (59.7)	15 (24.2)	10 (16.1)
Good Samaritan Hospital	Phoenix, Ariz.	57	34 (59.6)	12 (21.1)	11 (19.3)
Cedar's Sinai Hospital	Los Angeles, Calif.	27	15 (55.6)	8 (29.6)	4 (14.8)
Stanford University Medical Center	Palo Alto, Calif.	44	37 (84.1)	5 (11.4)	2 (4.5)
Kaiser Medical Center	Portland, Oreg.	61	48 (78.7)	9 (14.8)	4 (6.6)
Children's Hospital	Seattle, Wash.	37	24 (64.9)	8 (21.6)	5 (13.5)
Total		1,527	1,166 (76.4)	216 (14.1)	145 (9.5)

was near-complete cross-resistance among the three macrolides, with 97.6% of erythromycin-resistant strains also categorized as being resistant to azithromycin and clarithromycin.

The overall percentages of strains resistant to chloramphenicol, tetracycline, and TMP-SMX were 4.3, 7.5, and 18, respectively (Table 4). As was the case with the cephalosporins and macrolides, the resistance percentages with these agents were always higher with Pen^i isolates than with Pen^s strains and highest with Pen^r organisms. The resistance percentages among Pen^s, Pen^i, and Pen^r isolates were, respectively, 1, 7, and 32 with chloramphenicol, 0.3, 17, and 43 with tetracycline and 6, 40, and 80 with TMP-SMX.

Multiresistant strains are depicted in Table 5. A total of 138 study isolates (9.1%) were noted to be multiresistant when multiresistance was defined as Pen^i ($n = 49$) or Pen^r ($n = 89$) plus resistance to at least two of the following compounds: erythromycin, TMP-SMX, chloramphenicol and/or tetracycline. Two patterns of resistance were apparent among the multiresistant strains. Nearly all chloramphenicol-resistant strains were also resistant to either tetracycline (i.e., 61 of 67 [91%]) and/or TMP-SMX (i.e., 54 of 67 [80.6%]). The large majority of strains that were resistant to at least three if not all four of these non-β-lactam agents were also Pen^r, i.e., 58 of 79 (73.4%).

DISCUSSION

It is apparent from the results of this prospective national 30-center surveillance study that penicillin resistance with outpatient isolates of *S. pneumoniae* has emerged as a major problem in the United States. Although the percentages of Pen^i and Pen^r strains varied significant among different medical centers, the overall national percentage was 23.6, with approximately two of every five nonsusceptible strains manifesting Pen^r. As has been reported by others, the highest rates of penicillin resistance were noted with pneumococci from pediatric patients, in particular, those with infections such as otitis media or sinusitis, i.e., conditions often associated with extensive exposure to oral β-lactam antimicrobial agents and the resulting selective pressure (5, 14, 18). Both Pen^i and Pen^r strains were also, however, frequently recovered from adults in the present study, as has been previously reported (19).

Two previous multicenter national surveillance studies have been conducted in the United States since 1990, i.e., the period during which penicillin-resistant pneumococci apparently emerged as a major problem (2, 24). The first study, in 1991 to 1992, found 15.2% Pen^i and 2.6% Pen^r strains (24). The second study, in 1992 to 1993, observed percentages of 13.9 and

TABLE 2. Recovery of penicillin-resistant *S. pneumoniae* from patients grouped by age

Age group (yr)	Total no. of isolates	No. (%) of isolates that were penicillin:		
		Susceptible	Intermediate	Resistant
0–5	501	362 (72.3)	76 (15.2)	63 (12.6)
6–10	53	43 (81.1)	6 (11.3)	4 (7.5)
11–20	52	38 (73.1)	10 (19.2)	4 (7.7)
21–50	356	284 (79.8)	43 (12.1)	29 (8.1)
>50	560	437 (78.0)	79 (14.1)	44 (7.8)

TABLE 3. Recovery of penicillin-resistant *S. pneumoniae* from different specimen types

Specimen	Total no. of isolates	No. (%) of isolates that were penicillin:		
		Susceptible	Intermediate	Resistant
Middle ear fluid	118	68 (57.6)	26 (22.0)	24 (20.3)
Sinus aspirate	52	32 (61.5)	8 (15.4)	12 (23.1)
Conjuctival	105	93 (88.6)	10 (9.5)	2 (1.9)
Sputum	633	475 (75.0)	93 (14.7)	65 (10.3)
Blood	541	437 (80.8)	69 (15.8)	35 (6.5)
Cerebrospinal fluid	31	26 (83.9)	2 (7.7)	3 (9.7)
Other	43	31 (72.1)	8 (25.8)	4 (9.3)

7.3, respectively (2). The results of the current study indicate that the prevalence of Pen^i and Pen^r strains of *S. pneumoniae* continues to increase in the United States. Of perhaps even greater concern is the observation that the relative proportion of nonsusceptible strains composed of Pen^r organisms is also increasing. Currently, ca. 40% of nonsusceptible isolates are Pen^r. Obviously, this has major therapeutic implications insofar as Pen^r organisms are likely to be more refractory to management with penicillin irrespective of the infectious disease condition with which they are associated and are also most resistant to other β-lactam antimicrobial agents.

The results of this study also permit comparisons of the activities of other β-lactam antimicrobial agents versus contemporary pneumococci. Ampicillin was consistently 1 twofold dilution less active than penicillin. Amoxicillin and amoxicillin-clavulanate appeared to be essentially comparable to penicillin in activity. The enhanced activities of these two compounds versus penicillin for Pen^i and Pen^r *S. pneumoniae*, as has been previously described (22), was not observed in this study. Of interest were observations pertaining to resistance percentages with amoxicillin and amoxicillin-clavulanate against Pen^r strains, i.e., 66 and 60, respectively. These values indicate that a reasonably high percentage of Pen^r isolates of *S. pneumoniae* would be categorized as being something other than resistant to amoxicillin and amoxicillin-clavulanate according to current NCCLS breakpoints (17). Indeed, application of current breakpoints would give these two compounds the appearance of being more active than cefuroxime and nearly as active as cefotaxime and ceftriaxone against Pen^r organisms.

The cephalosporins could be separated into several groups with respect to in vitro activity as expressed by MIC_{50}s, MIC_{90}s, and geometric-mean MICs. Two oral agents, cephalexin and cefadroxil, had limited activity even for Pen^s *S. pneumoniae*. Three other oral cephalosporins, loracarbef, cefaclor, and cefixime, were generally active only against Pen^s strains. One agent, cefprozil, demonstrated at least modest activity versus Pen^i isolates in addition to being uniformly active against Pen^s strains. Two cephalosporins, cefuroxime and cefpodoxime, were, like cefprozil, active against Pen^s strains but demonstrated greater activity than cefprozil against Pen^i isolates. All three of these agents lacked activity against Pen^r isolates. Finally, two parenteral expanded-spectrum cephalosporins, cefotaxime and ceftriaxone, were nearly uniformly active against both the Pen^s and Pen^i strains and demonstrated at least some activity against Pen^r strains.

Resistance to cefotaxime and ceftriaxone has previously been described with *S. pneumoniae* (4, 7, 20). It has typically been observed with Pen^i strains and has been noted to be the

TABLE 4. In vitro activities of 23 antimicrobial agents for 1,527 outpatient isolates of *S. pneumoniae*[a]

Antimicrobial agent	Penicillin-susceptible strains (n = 1,165)				Penicillin-intermediate strains (n = 216)				Penicillin-resistant strains (n = 145)				All strains (n = 1,527)	
	MIC_{50}	MIC_{90}	Range of MICs	Mean MIC[b]	MIC_{50}	MIC_{90}	Range of MICs	Mean MIC	MIC_{50}	MIC_{90}	Range of MICs	Mean MIC	MIC_{50}	MIC_{90}
Penicillin	0.015	0.03	≤0.004–0.06	0.03	0.25	1	0.12–1	0.33	2	4	2–8	2.4	0.015	1
Ampicillin	0.034	0.06	≤0.008–1	0.03	0.5	2	0.06–4	0.51	4	8	2–16	4.0	0.03	2
Amoxicillin	0.015	0.03	<0.004–0.12	0.015	0.25	1	0.03–4	0.25	2	8	1–8	2.0	0.015	1
Amox-clav[c]	0.015	0.03	<0.004–1	0.015	0.25	1	0.03–4	0.25	2	4	1–8	2.0	0.015	1
Cefotaxime	0.015	0.06	<0.004–1	0.015	0.25	1	0.015–4	0.20	1	4	0.5–8	1.42	0.015	1
Ceftriaxone	0.03	0.06	≤0.004–1	0.024	0.25	1	0.008–4	0.25	2	4	0.5–8	1.46	0.03	1
Cefpodoxime	0.03	0.06	≤0.015–4	0.04	0.5	2	0.03–>16	0.58	4	16	1–>16	4.75	0.03	2
Cefuroxime	0.03	0.12	≤0.015–8	0.04	0.5	4	0.003–16	0.86	8	16	2–32	7.9	0.03	4
Cefprozil	0.25	0.25	≤0.03–16	0.20	1	8	0.12–32	1.5	16	32	4–64	18	0.25	8
Cefixime	0.25	0.5	≤0.06–32	0.31	4	16	0.12–128	3.5	32	64	8–>128	30	0.25	16
Cefaclor	0.5	1	≤0.06–128	0.71	4	64	0.12–>128	5.0	128	>128	16–>256	109	1	64
Loracarbef	1	2	≤0.06–128	1.0	8	64	0.5–>128	6.3	128	>128	8–>128	83	1	16
Cefadroxil	1	2	≤0.12–128	1.6	8	64	0.5–256	10.3	64	256	16–>256	145	2	64
Cephalexin	2	4	≤0.12–128	2.0	16	128	0.25–>256	14.2	128	>256	32–>256	141	2	128
Rifampin	0.03	0.06	≤0.015–>32	0.03	0.03	0.06	≤0.015–≥32	0.03	0.03	0.06	≤0.015–8	0.03	0.03	0.06
Vancomycin	0.25	0.5	≤0.015–1	0.35	0.25	0.5	0.12–1	0.34	0.25	0.5	0.25–1	0.33	0.25	0.5
Quino-dalfo[d]	1	2	0.12–4	0.97	1	2	0.25–8	1.2	1	2	0.5–4	1.2	1	2
Clarithromycin	≤0.03	0.06	≤0.03–>64	0.03	≤0.03	8	≤0.03–>64	0.07	0.06	>64	≤0.03–>64	2.0	≤0.03	1
Erythromycin	0.06	0.06	≤0.03–>64	0.06	0.06	8	≤0.03–>64	0.10	0.12	>64	≤0.03–>64	2.0	0.06	2
Azithromycin	0.12	0.12	≤0.03–>64	0.11	0.12	8	≤0.03–>64	0.23	0.25	>64	0.06–>64	3.5	0.12	2
Chloramphenicol	2	4	0.12–16	2.6	2	4	1–32	3.0	4	16	2–32	5.1	2	4
Tetracycline	0.12	0.25	≤0.03–64	0.17	0.12	32	0.06–64	0.35	0.25	32	0.06–32	0.89	0.12	0.25
TMP-SMX[e]	0.25	1	≤0.015–16	0.25	1	8	0.03–16	1.1	4	8	0.12–32	3.8	0.25	4

[a] All MICs given are in micrograms per milliliter.
[b] Geometric-mean MIC.
[c] Amox-clav, amoxicillin-clavulanate (2:1). The concentrations listed refer to amoxicillin.
[d] Quino-dalfo, quinopristin-dalfopristin (30:70). The concentrations listed refer to the total of the two streptogramins in the mixture.
[e] TMP-SMX, trimethoprim-sulfamethoxazole (1:19). The concentrations listed refer to trimethoprim.

TABLE 5. Multiply resistant *S. pneumoniae* recovered in a national, multicenter surveillance study which characterized 1,527 outpatient isolates

Resistance pattern (breakpoint [μg/ml])[a]				No. of isolates that were also[b]:			
Erythromycin (≥1)	TMP-SMX (≥4)	Chloramphenicol (≥8)	Tetracycline (≥8)	Pen^r	Pen^i	Pen^s	Total
R	S	S	S	0	9	16	25
S	R	S	S	37	48	55	140
S	S	R	S	1	1	1	3
S	S	S	R	1	5	6	12
R	R	S	S	24	16	20	60
R	S	R	S	1	0	0	1
R	S	S	R	2	10	3	15
S	R	R	S	0	0	0	0
S	R	S	R	0	8	2	10
S	S	R	R	4	0	1	5
R	R	R	S	1	1	0	2
R	R	S	R	15	1	5	21
R	S	R	R	4	0	0	4
S	R	R	R	15	9	0	24
R	R	R	R	23	4	1	28

[a] Organisms are noted as R (resistant) when their MICs were greater than or equal to the listed breakpoint; organisms are noted as S (susceptible) when their MICs were less than the listed breakpoint.

[b] Pen^r, high-level penicillin resistant; Pen^i, intermediate penicillin resistance; Pen^s, penicillin susceptible.

result of specific PBP alterations (7, 15). In the current study, fully 3.2% (cefotaxime) and 5.1% (ceftriaxone) of all study isolates had MICs of ≥2 μg/ml and thus were classified as resistant according to the criteria of the NCCLS (17). There was near-complete cross-resistance between these two agents, to wit, all cefotaxime-resistant isolates were also ceftriaxone resistant. Among the 1.9% of strains that were resistant to ceftriaxone but not resistant to cefotaxime, all but one had cefotaxime MICs of 1.0 μg/ml. The remaining isolate had a cefotaxime MIC of 0.5 μg/ml. It is not clear whether these apparent slight differences in activity between cefotaxime and ceftriaxone represent anything more than subtle in vitro differences in antibacterial effect. It is unlikely that they translate into meaningful differences in clinical utility. Also of interest in this study was the finding that the vast majority of strains resistant to cefotaxime and ceftriaxone were Pen^r, not Pen^i. For instance, among the total of 49 cefotaxime-resistant strains, 2 were Pen^i while 47 were Pen^r. Ceftriaxone resistance was observed with 78 isolates; 5 were Pen^i, and 73 were Pen^r.

One final observation concerning the activity of cephalosporins versus *S. pneumoniae* today in the United States pertains to the extent to which the activity of specific agents decreases for Pen^i and Pen^r strains versus Pen^s isolates. The drop in activity between Pen^s and Pen^i strains was 6- to 22-fold, depending on the individual cephalosporin considered. The same observation could be made of the cephalosporins when activity versus Pen^r strains was compared with the activity against Pen^i strains. Another 6- to 22-fold decrease in activity was observed. This information together with knowledge of the intrinsic activity of a particular cephalosporin versus Pen^s strains permits reasonably accurate predictions of the activity of that agent for Pen^i and Pen^r strains.

The three macrolides examined in this study, clarithromycin, erythromycin, and azithromycin, were characterized by comparable overall percentages of resistance of 10. The overall percentages of chloramphenicol, tetracycline, and TMP-SMX resistance were 4.3, 7.5, and 18, respectively. The percentages of resistance with all four of these antibiotic classes were significantly higher with Pen^r strains than with Pen^i isolates. Resistance was uncommon among Pen^s organisms. Clearly, as has been described previously, resistance to non-β-lactam agents, although mechanistically unrelated to penicillin resistance, occurs most commonly in the United States in strains of *S. pneumoniae* that are also β-lactam resistant (2, 21). Of significance was the observation that 9.1% of isolates of *S. pneumoniae* in this survey were Pen^i (3.2%) or Pen^r (5.9%) and also resistant to at least two of the following four antibiotics or antibiotic classes: macrolides, tetracycline, chloramphenicol, and TMP-SMX. Such isolates are considered multiresistant (10). Indeed, 23 isolates from 18 different centers were Pen^r and resistant to all four of the non-β-lactam agents noted above. Fourteen of these 23 organisms were also resistant to cefotaxime and ceftriaxone (MICs ≥2 μg/ml). Rifampin resistance (i.e., 0.5%) was uncommon.

Among the agents examined in this study, vancomycin was the only compound for which no resistant strains were recognized (MIC_{50}s and MIC_{90}s, 1 and 2 μg/ml, respectively). The quinopristin-dalfopristin combination was consistently active over a narrow concentration range (i.e., 0.25 to 4 μg/ml) with MIC_{50}s, MIC_{90}s, and geometric-mean MICs 4-fold higher than those noted with vancomycin. However, in the absence of accepted interpretive criteria, rates of resistance could not be calculated with this combination.

In conclusion, antimicrobial resistance has clearly emerged as a very serious problem with *S. pneumoniae* in the United States. By analogy based on experiences in other parts of the world, this problem is likely to grow in the future.

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