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Survey of Susceptibilities of *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* Isolates to 26 Antimicrobial Agents: a Prospective U.S. Study

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An antimicrobial susceptibility surveillance study of *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* isolates was performed during the winter of 1996–1997 in order to determine their susceptibilities to 5 fluoroquinolones and 21 other antimicrobial agents. Broth microdilution MICs were determined for 2,752 isolates from 51 U.S. medical centers. Of the 1,276 *S. pneumoniae* isolates, 64% were susceptible, 17% were intermediate, and 19% were highly resistant to penicillin. On the basis of the MICs at which 90% of isolates are inhibited and modal MICs, the hierarchy of the five fluoroquinolones from most to least active was grepafloxacin > sparfloxacin > levofloxacin = ciprofloxacin > ofloxacin. For *S. pneumoniae* isolates for which penicillin MICs were elevated, the MICs of the cephalosporins, macrolides, clindamycin, tetracycline, and trimethoprim-sulfamethoxazole were also elevated, but the MICs of the fluoroquinolones, vancomycin, and rifampin were not. The prevalence of penicillin-susceptible pneumococci varied by U.S. Bureau of the Census region (range, 44% in the East South Central region to 75% in the Pacific region). In addition, *S. pneumoniae* isolates from blood were significantly more susceptible to penicillin than those from respiratory, ear, or eye specimens, and pneumococci from patients ≤2 years old were significantly more resistant to penicillin than those from older patients (by chi-square analysis, $P < 0.05$). β-Lactamase was produced by 35% of *H. influenzae* isolates and 93% of *M. catarrhalis* isolates, resulting in increased MICs of amoxicillin and certain cephalosporins. We noted that the antimicrobial resistance patterns of *S. pneumoniae* isolates, which correlate with the penicillin susceptibility phenotype, vary by site of infection, age group of the patient, and geographic source of the isolate.

Over the past three decades, and particularly during the last decade, antimicrobial resistance among the common bacterial species that cause respiratory tract infections has increased (3–9, 16–18, 21). Current data indicate that approximately one-third of *Streptococcus pneumoniae* isolates in the United States have some level of resistance to penicillin (4, 21). Likewise, up to 40% of *Haemophilus influenzae* isolates and almost all *Moraxella catarrhalis* isolates produce β-lactamase, which mediates resistance to penicillins and certain cephalosporins (5, 6, 21). The observation that *S. pneumoniae* strains with decreased susceptibility to penicillin are often resistant to cephalosporins, macrolides, sulfonamides, and tetracyclines is also of concern (21).

A primary consideration in examining the impact of antimicrobial resistance on the therapy for respiratory tract infections is the fact that the majority of infections are treated empirically. Because most infections are observed among outpatients who are treated with oral formulations, assessment of resistance should study oral agents such as penicillins, cephalosporins, macrolides, trimethoprim-sulfamethoxazole (SXT), and several of the newer fluoroquinolones. In addition, because the resistance profiles of species such as *S. pneumoniae* can vary substantially depending on the geographic region, site of infection, and age of the patient from which the strains are isolated, an extensive and diverse collection of strains should be used to evaluate the activities of currently available antimicrobial agents (10, 17, 18, 21).

Although recent studies have examined resistance among these three species (7, 8, 11, 17, 18, 21), these studies generally have been smaller in scope in terms of the number of institutions involved and the number of strains collected and may not have examined patient age and site of infection for their relation to resistance prevalence. In this study, we assessed the susceptibilities of 2,752 recent clinical isolates of *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis* collected from 51 institutions in the United States to 26 antimicrobial agents. The 26 agents were selected to represent each of the major classes of antibiotics commonly used for empiric outpatient therapy, especially fluoroquinolones, which were absent from the most recent report in the surveillance literature on pneumococci (8).

(Portions of this work were presented in abstract form at the 37th Interscience Conference on Antimicrobial Agents and Chemotherapy [19] and the 6th International Symposium on New Quinolones and Related Antibiotics [20].)

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MATERIALS AND METHODS

Bacterial isolates. Each of the 51 laboratories that participated in the study was asked to contribute 30 consecutive, unique isolates of *S. pneumoniae* and *H. influenzae* and 15 isolates of *M. catarrhalis* from patients presenting to outpatient

clinics during 1996 and 1997. The laboratories were chosen to represent the nine regions designated by the U.S. Bureau of the Census: New England (two sites), Mid-Atlantic (four sites), South Atlantic (nine sites), East North Central (six sites), East South Central (three sites), West North Central (seven sites), West South Central (five sites), Mountain (eight sites), and Pacific (seven sites). Demographic data were collected for each patient from which an isolate was retrieved.

In addition to isolates from the upper respiratory tract (nasopharynx, middle ear fluid, and sinus), isolates from the trachea, bronchus, sputum, conjunctiva, cerebrospinal fluid, blood, and other specimen sources were accepted. Isolates were subcultured onto appropriate solid media and were sent to MRL laboratories for identification (1). All isolates were stored at −75°C or colder. Frozen isolates were thawed and were then subcultured onto blood agar to obtain good growth. These subcultures were used for susceptibility tests.

Antimicrobial agents. The 26 antimicrobial agents tested were both oral and parenteral drugs that have been used or considered as therapy for patients with upper respiratory tract infections. The panel of antimicrobial agents tested included two penicillins (penicillin and amoxicillin), one penicillin–β-lactamase inhibitor combination (amoxicillin-clavulanate), 10 oral and parenteral cephalosporins (cephalothin, cefaclor, loracarbef, cefuroxime, cefprozil, cefotaxime, ceftriaxone, cefpodoxime, cefixime, and ceftibuten), three macrolides (erythromycin, clarithromycin, and azithromycin), one lincosamide (clindamycin), five fluoroquinolones (ciprofloxacin, ofloxacin, levofloxacin, sparfloxacin, and grepafloxacin), and four miscellaneous drugs (vancomycin, rifampin, tetracycline, and SXT). These antimicrobial agents were obtained from the respective manufacturers as powders suitable for susceptibility testing.

Susceptibility testing. The MICs of the 26 antimicrobial agents were determined by the broth microdilution method as recommended by the National Committee for Clinical Laboratory Standards (NCCLS) (13, 14). MICs were determined by the microdilution method in Mueller-Hinton broth supplemented with 3 to 5% lysed horse blood for *S. pneumoniae*, in Haemophilus test medium for *H. influenzae* isolates, and in Mueller-Hinton broth supplemented with 3 to 5% sheep blood for *M. catarrhalis*. Inocula were prepared from overnight growth suspended in saline to achieve a turbidity equivalent to that of a 0.5 McFarland standard. The inoculated trays were incubated in ambient air for 20 to 24 h at 35°C. The MICs were read as the lowest concentration of antimicrobial agent that inhibited visible growth. *S. pneumoniae* ATCC 49619, *H. influenzae* ATCC 49247 and ATCC 49766, and *Staphylococcus aureus* ATCC 29213 were used as control organisms. For *S. pneumoniae* and *H. influenzae*, results were categorized according to NCCLS interpretive breakpoints (13). NCCLS has not yet published breakpoints for *M. catarrhalis*.

Statistical analysis. Data stratified by U.S. Bureau of the Census region, specimen source, and age group were compared by the chi-square test (Epilnfo, version 6; Centers for Disease Control and Prevention, Atlanta, Ga.). A P value of <0.05 was considered statistically significant.

RESULTS

The susceptibility data for 26 antimicrobial agents tested against *S. pneumoniae* strains collected from all institutions are given in Table 1 and are arranged according to penicillin susceptibility category. The MICs at which 50% of isolates are inhibited (MIC_{50}s) and MIC_{90}s were within ± 1 $\log_2$ concentration for the three penicillin compounds (penicillin, amoxicillin, and amoxicillin-clavulanate). Among the cephalosporins tested, the two parenteral, extended-spectrum cephalosporins (cefotaxime and ceftriaxone) were most active, with MIC_{90}s of 1.0 μg/ml. Cefpodoxime and cefuroxime were the most active oral cephalosporins tested, with MIC_{90}s of 2.0 and 4.0 μg/ml, respectively. However, the activities of all the β-lactam compounds varied notably with the activity of penicillin. For example, for penicillin-susceptible strains (MICs, ≤0.06 μg/ml) the ceftriaxone MIC_{90} was 0.06 μg/ml, with no resistant strains, but for penicillin-resistant strains (MICs, ≥2 μg/ml) the ceftriaxone MIC_{90} was 4.0 μg/ml and 32% of the strains were resistant. Although the in vitro activities of ceftriaxone, cefotaxime, cefpodoxime, and cefuroxime against penicillin-nonsusceptible groups were diminished, these four cephalosporins were more active than the other cephalosporins tested.

Resistance to non-β-lactams among penicillin-susceptible strains was observed for all three macrolides (erythromycin, azithromycin, and clarithromycin), clindamycin, SXT, and tetracycline, but the levels of resistance to all of these agents increased substantially for the penicillin-intermediate (MICs, between 0.12 and 1 μg/ml) and penicillin-resistant strains. For example, the prevalence of macrolide-resistant strains was 10 times greater for penicillin-resistant strains (range, 68.4 to 68.9%) than for penicillin-susceptible strains (range, 6.0 to 6.3%). The activities of vancomycin, rifampin, and each of the fluoroquinolones did not vary by the penicillin susceptibility status of the isolates. No strains were resistant to vancomycin, and only 0.2% were resistant to grepafloxacin, sparfloxacin, ofloxacin, or levofloxacin. (NCCLS has not yet established interpretive breakpoints for ciprofloxacin.)

Because NCCLS interpretive breakpoints are not available for all cephalosporins, examination of MIC distributions is the only way to achieve a detailed comparison of their relative activities (Table 2). For ceftriaxone, cefotaxime, cefpodoxime, and cefuroxime, the modal MICs were ≤0.03 μg/ml and were the lowest among all cephalosporins tested. Four cephalosporins (cefaclor, loracarbef, cefixime, and ceftibuten) had MIC_{90}s of >8 μg/ml.

MIC distribution data for the quinolones and macrolides are given in Table 3. Because resistance to the fluoroquinolones remains uncommon (Table 1), distribution data were used to set benchmarks for any subtle but significant changes that may occur in pneumococcal populations before interpretive breakpoints are breached. On the basis of the MIC_{90}s and the modal MICs, the hierarchy of these five agents from most active to least active was grepafloxacin (MIC_{90} = 0.25 μg/ml, modal MIC = 0.12 μg/ml), sparfloxacin (MIC_{90} = 0.25 μg/ml, modal MIC = 0.25 μg/ml), levofloxacin (MIC_{90} = 1 μg/ml, modal MIC = 0.5 μg/ml) and ciprofloxacin (MIC_{90} = 1 μg/ml, modal MIC = 0.5 μg/ml), and ofloxacin (MIC_{90} = 2 μg/ml, modal MIC = 1.0 μg/ml). The modal MICs of grepafloxacin and levofloxacin were 3 doubling dilutions lower than their respective intermediate breakpoints of 1.0 and 4.0 μg/ml. The modal MICs of sparfloxacin and ofloxacin were 2 doubling dilutions below their respective breakpoints of 1.0 and 4.0 μg/ml.

The MIC_{90}s of erythromycin, clarithromycin, and azithromycin were within 1 doubling dilution of each other (between 8 and 16 μg/ml) (Table 3). The modal MICs of clarithromycin, erythromycin, and azithromycin were ≤0.03, 0.06, and 0.12 μg/ml, respectively. When the activities of the macrolides and clindamycin were compared, 74% of 301 macrolide-resistant strains were susceptible to clindamycin.

Susceptibility data for pneumococci were analyzed according to the nine regions established by the U.S. Bureau of the Census (Table 4). The highest percentage of penicillin-susceptible isolates occurred in the Pacific (74.5%) and East North Central (72.2%) regions. For all penicillins and cephalosporins, the lowest in vitro activity was among strains from the East South Central region, where only 43.8% of strains were susceptible to penicillin, compared to the average of 64.3% for all U.S. regions combined. For all agents but tetracycline, the prevalence of susceptible pneumococci was lowest in the East South Central region. While the prevalence of macrolide-susceptible isolates varied notably among the nine regions (from 53.1 to 96.5%), clindamycin susceptibility prevalences fluctuated within a narrow range of 91.2% (Mid-Atlantic) to 96.5% (New England). Due to the high activity levels of vancomycin (no nonsusceptible isolates) and the fluoroquinolones (a total of five nonsusceptible strains were isolated in the New England, South Atlantic, West South Central, and Pacific regions), these data were not compared in Table 4.

The differences in *S. pneumoniae* susceptibility according to specimen source are shown in Table 5. Regardless of the class of antimicrobial agent examined, isolates from the ear were not as likely to be susceptible as strains from other specimen sources. For example, 44.7% of ear isolates were penicillin susceptible, but >60% of blood and cerebrospinal fluid, respi-

TABLE 1. Susceptibility of *S. pneumoniae* to 26 antimicrobial agents

Antimicrobial agent and phenotype (no. of isolates)[a]	MIC (μg/ml)			Percent[b]		
	Range	50%	90%	S	I	R
Amoxicillin						
All (1,274)	≤0.06–16	≤0.06	2.0	80.5	8.1	11.5
Pen S (818)	≤0.06–1	≤0.06	≤0.03	99.9	0.1	0.0
Pen I (218)	≤0.06–4	0.25	1.0	83.9	11.9	4.1
Pen R (238)	0.5–16	2.0	4.0	10.5	31.9	57.6
Amoxicillin-clavulanate						
All (1,269)	≤0.03–16	≤0.03	2.0	77.7	11.3	11.0
Pen S (816)	≤0.03–1	≤0.03	≤0.03	99.9	0.1	0.0
Pen I (217)	≤0.03–4	0.25	1.0	77.9	18.9	3.2
Pen R (236)	0.5–16	2.0	4.0	0.8	42.8	56.4
Penicillin						
All (1,276)	0.008–>8	0.03	2.0	64.3	17.1	18.7
Pen S (820)	0.008–0.06	0.03	0.03	100.0	0.0	0.0
Pen I (218)	0.12–1	0.25	1.0	0.0	100.0	0.0
Pen R (238)	2–>8	2.0	4.0	0.0	0.0	100.0
Cephalothin[c]						
All (1,276)	≤0.03–>64	0.25	8.0			
Pen S (820)	≤0.03–8	0.12	0.25			
Pen I (218)	0.06–16	1.0	4.0			
Pen R (238)	1–>64	8.0	32			
Cefaclor[c]						
All (1,275)	0.03–>32	0.5	>32			
Pen S (820)	0.03–>32	0.5	1.0			
Pen I (218)	0.25–>32	4.0	>32			
Pen R (237)	1–>32	>32	>32			
Loracarbef[c]						
All (1,273)	0.06–>32	1.0	>32			
Pen S (817)	0.06–>32	1.0	2.0			
Pen I (218)	0.25–>32	4.0	>32			
Pen R (238)	1–>32	>32	>32			
Cefuroxime						
All (1,275)	≤0.03–>32	≤0.03	4.0	72.1	3.4	24.5
Pen S (820)	≤0.03–8	≤0.03	0.25	99.1	0.4	0.5
Pen I (218)	≤0.03–32	1.0	4.0	46.8	18.3	34.9
Pen R (237)	0.25–>32	4.0	16	1.7	0.0	98.3
Cefprozil[c]						
All (1,274)	0.03–>32	0.25	8.0			
Pen S (818)	0.03–8	0.12	0.5			
Pen I (218)	0.06–32	1.0	4.0			
Pen R (238)	0.5–>32	8.0	32			
Cefpodoxime[c]						
All (1,274)	≤0.015–>32	0.03	2.0			
Pen S (818)	≤0.015–2	0.03	0.06			
Pen I (218)	0.03–32	0.5	2.0			
Pen R (238)	0.06–>32	2.0	8.0			
Cefixime[c]						
All (1,275)	≤0.25–>8	≤0.25	>8			
Pen S (819)	≤0.25–>8	≤0.25	0.5			
Pen I (218)	≤0.25–>8	4.0	>8			
Pen R (238)	1–>8	>8	>8			
Ceftibuten[c]						
All (1,275)	≤0.25–>8	4.0	>8			
Pen S (819)	≤0.25–>8	4.0	>8			
Pen I (218)	≤0.25–>8	>8	>8			
Pen R (238)	8–>8	>8	>8			

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TABLE 1—*Continued*

Antimicrobial agent and phenotype (no. of isolates)[a]	MIC (μg/ml)			Percent[b]		
	Range	50%	90%	S	I	R
Cefotaxime						
All (1,276)	≤0.015–32	0.03	1.0	79.9	13.6	6.5
Pen S (820)	≤0.015–1	≤0.015	0.06	99.9	0.1	0.0
Pen I (218)	≤0.015–8	0.25	1.0	85.3	11.0	3.7
Pen R (238)	0.06–32	1.0	4.0	5.9	62.6	31.5
Ceftriaxone						
All (1,274)	≤0.015–>32	0.03	1.0	80.7	12.9	6.4
Pen S (818)	≤0.015–1	≤0.015	0.06	99.9	0.1	0.0
Pen I (218)	≤0.015–4	0.25	1.0	85.8	11.0	3.2
Pen R (238)	0.03–>32	1.0	4.0	10.1	58.4	31.5
Erythromycin						
All (1,276)	≤0.03–>64	0.06	8.0	76.4	0.3	23.3
Pen S (820)	≤0.03–>64	0.06	0.06	93.5	0.1	6.3
Pen I (218)	≤0.03–>64	0.06	>64	61.9	0.9	37.2
Pen R (238)	≤0.03–>64	4.0	>64	30.7	0.4	68.9
Azithromycin						
All (1,275)	0.06–>64	0.12	16	77.0	0.2	22.8
Pen S (820)	0.06–>64	0.12	0.25	93.7	0.0	6.3
Pen I (218)	0.06–>64	0.12	>64	64.2	0.5	35.3
Pen R (237)	0.06–>64	8.0	>64	31.2	0.4	68.4
Clarithromycin						
All (1,275)	≤0.03–>64	≤0.03	8.0	76.7	0.5	22.7
Pen S (820)	≤0.03–>64	≤0.03	0.06	93.7	0.4	6.0
Pen I (218)	≤0.03–>64	≤0.03	>64	61.9	1.8	36.2
Pen R (237)	≤0.03–>64	2.0	>64	31.6	0.0	68.4
Clindamycin						
All (1,276)	≤0.015–>32	0.06	0.12	93.6	0.2	6.3
Pen S (820)	≤0.015–>32	0.06	0.12	98.8	0.1	1.1
Pen I (218)	0.03–>32	0.06	>32	86.7	0.0	13.3
Pen R (238)	0.03–>32	0.06	>32	81.9	0.4	17.6
Grepafloxacin						
All (1,275)	0.004–8	0.12	0.25	99.8	0.0	0.2
Pen S (820)	0.004–2	0.12	0.25	99.9	0.0	0.1
Pen I (218)	0.015–8	0.12	0.25	99.5	0.0	0.5
Pen R (237)	0.06–4	0.12	0.12	99.6	0.0	0.4
Sparfloxacin						
All (1,276)	0.015–>8	0.25	0.25	99.6	0.2	0.2
Pen S (820)	0.015–1	0.25	0.25	99.8	0.2	0.0
Pen I (218)	0.06–>8	0.25	0.25	99.5	0.0	0.5
Pen R (238)	0.06–2	0.25	0.25	99.2	0.0	0.8
Levofloxacin						
All (1,276)	0.008–>8	0.5	1.0	99.8	0.1	0.2
Pen S (820)	0.008–2	0.5	1.0	100.0	0.0	0.0
Pen I (218)	0.5–>8	0.5	1.0	99.5	0.0	0.5
Pen R (238)	0.25–8	0.5	1.0	99.2	0.4	0.4
Ciprofloxacin[d]						
All (1,275)	0.004–>8	0.5	1.0			
Pen S (820)	0.004–4	0.5	1.0			
Pen I (218)	0.015–>8	0.5	1.0			
Pen R (237)	0.12–>8	0.5	1.0			
Ofloxacin						
All (1,275)	0.008–>8	1.0	2.0	99.6	0.2	0.2
Pen S (820)	0.008–4	1.0	2.0	99.8	0.2	0.0
Pen I (218)	0.008–>8	1.0	2.0	99.5	0.0	0.5
Pen R (237)	0.25–>8	1.0	2.0	99.2	0.4	0.4

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TABLE 1—*Continued*

Antimicrobial agent and phenotype (no. of isolates)[a]	MIC (μg/ml)			Percent[b]		
	Range	50%	90%	S	I	R
Rifampin						
All (1,276)	≤0.015–>16	0.03	0.03	99.8	0.0	0.2
Pen S (820)	≤0.015–>16	0.03	0.03	99.8	0.0	0.2
Pen I (218)	≤0.015–0.25	0.03	0.03	100.0	0.0	0.0
Pen R (238)	≤0.015–4	0.03	0.03	99.6	0.0	0.4
Tetracycline						
All (1,273)	≤0.5–>4	≤0.5	>4	83.1	0.3	16.6
Pen S (819)	≤0.5–>4	≤0.5	≤0.5	96.0	0.2	3.8
Pen I (218)	≤0.5–>4	≤0.5	>4	72.0	0.9	27.1
Pen R (236)	≤0.5–>4	>4	>4	48.7	0.0	51.3
SXT						
All (1,268)	≤0.125–>4	0.25	>4	88.1	0.0	11.9
Pen S (817)	≤0.125–>4	≤0.125	1.0	96.7	0.0	3.3
Pen I (216)	≤0.125–>4	1.0	>4	86.6	0.0	13.4
Pen R (235)	≤0.125–>4	4.0	>4	59.6	0.0	40.4
Vancomycin						
All (1,275)	0.12–0.5	0.25	0.25	100.0	0.0	0.0
Pen S (820)	0.12–0.5	0.25	0.25	100.0	0.0	0.0
Pen I (217)	0.12–0.5	0.25	0.25	100.0	0.0	0.0
Pen R (238)	0.25–0.5	0.25	0.25	100.0	0.0	0.0

[a] Analysis by all isolates, penicillin-susceptible isolates (Pen S) isolates, penicillin-intermediate (Pen I) isolates, and penicillin-resistant (Pen R) isolates.
[b] Percent susceptible (S), intermediate (I), and resistant (R) according to NCCLS breakpoints.
[c] Breakpoints are not available for most oral cephalosporins and are being established or revised by NCCLS.
[d] NCCLS breakpoints not available for the fluoroquinolone ciprofloxacin.

ratory, and eye isolates were penicillin susceptible. Nonsusceptibility was second most common among respiratory isolates, and the rare fluoroquinolone-resistant and rifampin-resistant isolates were from the respiratory tract. With few exceptions, the prevalence of susceptible isolates from blood and cerebrospinal fluid specimens was significantly greater than the prevalence of susceptible isolates from respiratory, ear, or eye specimens ($P < 0.05$).

S. pneumoniae antimicrobial susceptibility also was stratified by patient age group (Table 6). For β-lactams, macrolides, clindamycin, and tetracycline, the prevalence of susceptible strains was lowest among isolates from patients who were ≤2 years of age. For all agents listed in Table 6, the differences in the prevalences of susceptible strains between the ≤2-year-old age group and the ≥13-year-old age group were significant ($P < 0.05$). All of the fluoroquinolone-nonsusceptible strains were isolated from patients ≥13 years of age.

A summary of the susceptibilities of the *H. influenzae* isolates to 23 antimicrobial agents is shown in Table 7. β-Lactamase was produced by 35% of the *H. influenzae* strains. Of the 359 isolates that produced β-lactamase, 2 isolates would be categorized as amoxicillin susceptible if the NCCLS breakpoints for ampicillin were applied. One β-lactamase-negative, amoxicillin-clavulanate-resistant strain was encountered. Resistance to cefaclor, loracarbef, and cefprozil was common among β-lactamase-producing strains, but resistance to the other cephalosporins was rare or not encountered, regardless of the β-lactamase production status of the strains studied. Azithromycin was the most active macrolide against *H. influenzae*, with the azithromycin MIC_{90} being 2.0 μg/ml and 99.7% of isolates being susceptible to azithromycin, whereas the clarithromycin MIC_{90} was 8 μg/ml and 91.7% of isolates were susceptible to clarithromycin. Tetracycline resistance was uncommon (0.8%), but 10.2% of the isolates were resistant to SXT. No fluoroquinolone-nonsusceptible strains were isolated.

Of the 444 *M. catarrhalis* isolates, 93.7% produced β-lactamase. Because NCCLS does not recommend interpretive categories for *M. catarrhalis*, we relied on MICs to assess antimicrobial activity. For the β-lactamase-positive isolates the amoxicillin MIC_{90} was 16 μg/ml, while for β-lactamase-negative isolates the MIC_{90} was 0.25 μg/ml, a 64-fold difference (Table 8). For the other β-lactams, the effect of β-lactamase production on the MIC_{90}s was much less dramatic, usually a twofold or fourfold difference. The fluoroquinolones, macrolides, and SXT were all highly active against the *M. catarrhalis* strains studied.

DISCUSSION

The results from this in vitro study confirm and extend those from previous surveillance studies but, in addition, present data for most of the agents that might be considered as therapy for infections caused by *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*. Of these organisms, the greatest recent increases in resistance have occurred in *S. pneumoniae*. A study performed in the early 1990s found that 17.8% of isolates had some level of nonsusceptibility to penicillin, with 2.6% having high-level resistance (MIC, ≥2.0 μg/ml) (16). By 1996 and 1997, the penicillin susceptibility profile changed dramatically in the United States, with 33.5% of 9,190 isolates reported to be nonsusceptible, of which 13.6% had high-level resistance (21). Doern et al. (8) reported that 43.8% of 845 pneumococci isolated in 1997 were not susceptible, with 16% having high-level resistance. The data from this 1996–1997 study involving 1,276 pneumococci show that the overall penicillin nonsusceptibility was 35.7%, with 18.7% having high-level resistance. In

TABLE 3. MICs of fluoroquinolones and macrolides for *S. pneumoniae*

Antimicrobial class and agent (no. of strains)	% (cumulative %) of strains for which the MIC (μg/ml) is as follows:											
	≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	≥64
Fluoroquinolones												
Grepafloxacin (1,275)	0.5 (0.5)	14.4 (14.9)	71.8 (86.7)	**12.3 (99.0)**[a]	0.8 (99.8)	0.1 (99.8)	0.1 (99.8)	0.1 (99.9)	0.1 (100)			
Sparfloxacin (1,276)	0.1 (0.1)	0.5 (0.6)	17.6 (18.2)	**75.7 (93.9)**	5.6 (99.5)	0.2 (99.7)	0.2 (99.9)	0.0 (99.9)	0.0 (99.9)	0.1 (100.0)		
Levofloxacin (1,274)	0.1 (0.1)	0.0 (0.1)	0.1 (0.2)	0.2 (0.4)	65.4 (65.8)	**33.6 (99.4)**	0.4 (99.8)	0.1 (99.9)	0.1 (99.99)	0.1 (100.0)		
Ciprofloxacin (1,275)	0.1 (0.1)	0.0 (0.1)	0.4 (0.5)	10.1 (10.6)	61.3 (71.9)	**24.6 (96.5)**	3.0 (99.5)	0.3 (99.8)	0.0 (99.8)	0.2 (100.0)		
Ofloxacin (1,275)	0.2 (0.2)	0.1 (0.3)	0.1 (0.4)	0.2 (0.6)	0.8 (1.4)	79.7 (81.1)	**18.5 (99.6)**	0.2 (99.8)	0.0 (99.8)	0.2 (100.0)		
Macrolides												
Erythromycin (1,276)	27.3 (27.3)	46.8 (74.1)	2.0 (76.1)	0.3 (76.4)	0.3 (76.7)	0.7 (77.4)	1.7 (79.1)	5.8 (84.9)	**5.5 (90.4)**	3.8 (94.2)	0.4 (94.6)	5.4 (100.0)
Clarithromycin (1,275)	69.6 (69.6)	6.3 (75.9)	0.5 (76.4)	0.3 (76.7)	0.5 (77.2)	1.5 (78.7)	5.5 (84.2)	4.8 (89.0)	**4.6 (93.6)**	1.2 (94.8)	0.3 (95.1)	4.9 (100.0)
Azithromycin (1,275)		7.2 (7.2)	58.6 (65.8)	10.9 (76.7)	0.3 (77.0)	0.2 (77.2)	1.0 (78.2)	2.2 (80.4)	5.5 (85.9)	**4.8 (90.7)**	3.1 (93.8)	6.2 (100.0)

[a] Values in boldface indicate percentage (cumulative percentage) of strains for which the MIC is the MIC_{90}.

TABLE 2. MICs of cephalosporins for *S. pneumoniae* isolates

Antimicrobial agent (no. of strains)	% (cumulative %) of strains for which the MIC (μg/ml) is as follows:											
	≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	≥64
Ceftriaxone (1,274)	63.6 (63.6)	7.1 (70.7)	3.6 (74.3)	4.4 (78.7)	6.3 (85.0)	**10.8 (95.8)**[a]	2.8 (98.6)	1.3 (99.9)	0.1 (99.9)	0.0 (99.9)	0.0 (99.9)	0.1 (100.0)[b]
Cefotaxime (1,276)	59.7 (59.7)	7.3 (67.0)	5.5 (72.5)	5.4 (77.9)	9.2 (87.1)	**9.5 (96.6)**	1.9 (98.5)	0.6 (99.1)	0.8 (99.9)	0.0 (99.9)	0.1 (100.0)[b]	
Cefpodoxime (1,274)	53.9 (53.9)	6.8 (60.7)	6.6 (67.3)	3.8 (71.1)	3.1 (74.3)	4.7 (79.0)	**14.7 (93.6)**	3.0 (96.6)	1.4 (98.0)	1.7 (99.8)	0.2 (99.9)	0.1 (100.0)
Cefuroxime (1,275)	25.1 (25.1)	2.1 (27.2)	1.8 (29.0)	13.1 (42.1)	23.9 (66.0)	14.2 (80.2)	8.6 (88.8)	**7.2 (96.0)**	2.4 (98.4)	0.8 (99.2)	0.7 (99.9)	0.1 (100.0)[c]
Cephalothin (1,276)	0.1 (0.1)	4.3 (4.4)	45.0 (49.4)	11.4 (60.7)	10.9 (71.6)	3.7 (75.3)	3.8 (79.1)	5.6 (84.7)	**7.6 (92.3)**	5.3 (97.6)	1.8 (99.4)	0.6 (100.0)
Cefprozil (1,274)	0.3 (0.3)	11.9 (12.2)	23.2 (35.3)	21.6 (56.9)	11.5 (68.4)	4.6 (72.9)	4.2 (77.1)	5.3 (82.4)	**10.0 (92.4)**	4.4 (96.8)	2.7 (99.5)	0.5 (100.0)
Ceftibuten (1,275)				0.4 (0.4)[d]	0.5 (0.9)	0.7 (1.6)	8.6 (10.3)	40.1 (50.4)	9.3 (59.6)	**40.4 (100.0)**[e]		
Cefixime (1,275)				54.1 (54.1)[d]	7.8 (62.0)	4.6 (66.6)	3.8 (70.4)	3.5 (73.9)	3.4 (77.3)	**22.7 (100.0)**[e]		
Cefaclor (1,275)	0.1 (0.1)	0.2 (0.2)	0.9 (1.2)	27.2 (28.4)	25.6 (54.0)	14.5 (68.5)	4.2 (72.8)	1.8 (74.6)	1.6 (76.2)	1.5 (77.7)	3.1 (80.9)	**19.1 (100.0)**
Loracarbef (1,273)		0.1 (0.1)	0.2 (0.2)	1.0 (1.3)	22.5 (23.7)	32.0 (55.7)	14.8 (70.5)	2.7 (73.3)	2.0 (75.3)	0.8 (76.0)	2.0 (78.0)	**22.0 (100.0)**

[a] Values in boldface indicate percentage (cumulative percentage) of strains for which the MIC is the MIC_{90}.
[b] The MICs of ceftriaxone and cefotaxime for one strain were >4 μg/ml.
[c] The MIC of cefuroxime for one strain was ≥64 μg/ml.
[d] The lowest concentration tested was 0.25 μg/ml.
[e] The highest concentration tested was 16 μg/ml.

TABLE 4. Antimicrobial susceptibility of *S. pneumoniae* isolates by nine regions of the United States[a]

Antimicrobial agent	% Susceptible[b]									
	New England (n = 57)	Mid-Atlantic (n = 125)	South Atlantic (n = 205)	East North Central (n = 158)	East South Central (n = 32)	West North Central (n = 172)	West South Central (n = 143)	Mountain (n = 198)	Pacific (n = 184)	United States (n = 1294)
Penicillin	68.4	64.0	60.7	72.2	43.8[c]	61.0	56.3	63.1	74.5[c]	64.3
Amoxicillin	84.2	74.4	80.0	88.6[c]	65.6[c]	73.8[c]	76.2	78.8	90.8[c]	80.5
Amoxicillin-clavulanate	82.1	73.6	75.1	86.1[c]	62.5[c]	71.9	72.3	75.1	89.7[c]	77.7
Ceftriaxone	82.5	73.6	79.0	89.9[c]	68.8	77.9	75.5	77.8	90.8[c]	80.7
Erythromycin	84.2	77.6	75.7	77.8	53.1[c]	73.8	68.8[c]	77.3	84.2[c]	76.4
Clindamycin	96.5	91.2	92.2	96.2	93.8	93.6	93.1	94.4	92.9	93.6
SXT	91.2	92.6	88.3	92.4	77.4	82.6[c]	76.9[c]	87.8	96.2[c]	88.1
Tetracycline	84.2	74.4	85.3	88.6	81.3	86.1	85.2	78.3	82.6	83.1

[a] These regions are defined by the U.S. Bureau of the Census: New England (Maine, Massachusetts, New Hampshire, Rhode Island, Vermont, Connecticut), Mid-Atlantic (New Jersey, New York, Pennsylvania), South Atlantic (North Carolina, Georgia, Florida, West Virginia, District of Columbia, South Carolina, Maryland, Delaware, Virginia), East North Central (Wisconsin, Illinois, Indiana, Michigan, Ohio), East South Central (Alabama, Kentucky, Mississippi, Tennessee), West North Central (Kansas, Iowa, Minnesota, Nebraska, South Dakota, North Dakota, Missouri), West South Central (Texas, Louisiana, Arkansas, Oklahoma), Mountain (Montana, Nevada, Wyoming, Utah, Idaho, Arizona, Colorado, New Mexico), and Pacific (Washington, Alaska, California, Hawaii, Oregon).

[b] Susceptible by using the interpretive categories recommended by NCCLS.

[c] A significant difference exists ($P < 0.05$) between the antimicrobial susceptibility for this region and the overall prevalence for the United States.

TABLE 5. Antimicrobial susceptibility of *S. pneumoniae* by specimen source[a]

Antimicrobial agent	% Susceptible[b]			
	Blood/CSF[c] (n = 370)	Respiratory tract (n = 682)	Ear (n = 85)	Eye (n = 58)
Penicillin	77.8	60.9[d]	44.7[d]	65.5[d]
Amoxicillin	89.7	79.0[d]	58.8[d]	82.5
Amoxicillin-clavulanate	87.2	76.3[d]	55.3[d]	78.9
Ceftriaxone	88.4	79.9[d]	60.0[d]	84.2
Erythromycin	85.4	72.9[d]	65.9[d]	79.3
Clindamycin	96.5	93.8	88.2[d]	87.9[d]
SXT	92.7	86.6[d]	77.4[d]	93.0
Tetracycline	90.8	81.1[d]	76.2[d]	77.2[d]

[a] Of the 1,276 isolates, 81 were from specimen sources other than blood or cerebrospinal fluid, respiratory tract, ear, or eye and were thus excluded from this analysis.

[b] Susceptible by using the interpretive categories recommended by NCCLS.

[c] In addition to blood and cerebrospinal fluid (CSF), samples from other sterile sites may have been included.

[d] The prevalence of susceptible strains was significantly lower ($P < 0.05$) than that for the blood or cerebrospinal fluid referent group.

addition, this study with 26 antimicrobial agents suggests that the activities of many penicillins, cephalosporins, macrolides, lincosamides, tetracyclines, and sulfonamides against *S. pneumoniae* may be compromised because of an association with penicillin resistance.

The level of susceptibility to cephalosporins among pneumococci in this study appeared to be slightly lower than those presented in recent reports of studies with 1996–1997 isolates (8, 21). Doern et al. (8) reported that 86.2% of strains were susceptible to cefotaxime, Thornsberry and colleagues (21) found that 87.1% were susceptible to ceftriaxone, and this study found that 79.9% were susceptible to cefotaxime and 80.7% were susceptible to ceftriaxone. Because of the potential changes to current NCCLS interpretive category breakpoints for cephalosporins, examination of cephalosporin activity by MIC distribution is important (Table 2). Analyses of these activities on the basis of MIC distribution data provide direct comparisons that are not restricted by occasional adjustments to interpretive breakpoints.

Macrolide susceptibility in this study, which ranged between 76.4 and 77.0%, was lower than that reported by other studies with recent isolates, which ranged between 81% (21) and 86% (8). Similarly, our result for clindamycin susceptibility (93.6%)

TABLE 6. Antimicrobial susceptibility of *S. pneumoniae* by age group[a]

Antimicrobial agent	% Susceptible[b]		
	≤2 yr (n = 284)	3–12 yr (n = 134)	≥13 yr (n = 813)
Penicillin	48.6	61.2[c]	70.3[c]
Amoxicillin	68.0	74.4	85.5[c]
Amoxicillin-clavulanate	62.4	72.9[c]	83.5[c]
Ceftriaxone	66.9	76.7[c]	85.9[c]
Erythromycin	65.5	74.6	80.3[c]
Clindamycin	87.3	94.8[c]	95.7[c]
SXT	82.3	81.1	91.1[c]
Tetracycline	77.1	86.5[c]	84.9[c]

[a] Forty-five isolates were not available for this analysis.

[b] Susceptible by using the interpretive categories recommended by NCCLS.

[c] The prevalence of susceptible strains is significantly higher than the prevalence in the ≤2-year-old age group ($P < 0.05$).

TABLE 7. Susceptibility of *H. influenzae* to 23 antimicrobial agents

Antimicrobial agent and phenotype (no. of isolates)[a]	MIC (μg/ml)			Percent[b]		
	Range	50%	90%	S	I	R
Amoxicillin[c]						
All (1,031)	≤0.03–>16	0.5	>16	61.0	5.5	33.5
β-Lactamase+ (359)	0.5–>16	>16	>16	0.6	5.3	94.2
β-Lactamase− (672)	≤0.03–8	0.5	1.0	93.3	5.7	1.0
Amoxicillin-clavulanate						
All (1,031)	≤0.03–8	0.5	1.0	99.9	0.0	0.1
β-Lactamase+ (359)	≤0.03–2	0.5	2.0	100.0	0.0	0.0
β-Lactamase− (672)	≤0.03–8	0.25	0.5	99.9	0.0	0.1
Cephalothin[d]						
All (1,029)	≤0.03–>64	2.0	16			
β-Lactamase+ (359)	0.06–>64	8.0	32			
β-Lactamase− (670)	≤0.03–64	1.0	8.0			
Cefaclor						
All (1,032)	≤0.03–>32	2.0	8.0	90.1	3.9	6.0
β-Lactamase+ (360)	≤0.03–>32	4.0	32	76.9	7.5	15.6
β-Lactamase− (672)	≤0.03–32	2.0	4.0	97.2	1.9	0.9
Loracarbef						
All (1,031)	0.03–>32	1.0	8.0	93.2	2.1	4.7
β-Lactamase+ (359)	0.25–>32	4.0	32	81.3	5.6	13.1
β-Lactamase− (672)	0.03–32	1.0	2.0	99.6	0.3	0.1
Cefuroxime						
All (1,031)	≤0.03–>32	0.5	1.0	99.2	0.7	0.1
β-Lactamase+ (359)	≤0.03–>32	0.5	1.0	99.2	0.6	0.3
β-Lactamase− (672)	≤0.03–8	0.5	1.0	99.3	0.7	0.0
Cefprozil						
All (1,031)	0.12–>32	4.0	32	79.6	8.2	12.1
β-Lactamase+ (359)	0.25–>32	8.0	>32	51.5	16.2	32.3
β-Lactamase− (672)	0.12–32	2.0	8.0	94.6	4.0	1.3
Cefpodoxime						
All (1,031)	≤0.015–2	0.06	0.25	100.0	0.0	0.0
β-Lactamase+ (359)	≤0.015–1	0.06	0.25	100.0	0.0	0.0
β-Lactamase− (672)	≤0.015–2	0.06	0.25	100.0	0.0	0.0
Cefixime						
All (1,031)	≤0.25–1	≤0.25	≤0.25	100.0	0.0	0.0
β-Lactamase+ (359)	≤0.25–1	≤0.25	≤0.25	100.0	0.0	0.0
β-Lactamase− (672)	≤0.25–1	≤0.25	≤0.25	100.0	0.0	0.0
Ceftibuten						
All (1,031)	≤0.25–>8	≤0.25	≤0.25	99.9	0.0	0.1
β-Lactamase+ (359)	≤0.25–8	≤0.25	≤0.25	99.7	0.0	0.3
β-Lactamase− (672)	≤0.25–2	≤0.25	0.5	100.0	0.0	0.0
Cefotaxime						
All (1,029)	≤0.015–2	≤0.015	0.03	100.0	0.0	0.0
β-Lactamase+ (359)	≤0.015–1	≤0.015	0.03	100.0	0.0	0.0
β-Lactamase− (670)	≤0.015–2	≤0.015	0.03	100.0	0.0	0.0
Ceftriaxone						
All (1,030)	≤0.015–0.5	≤0.015	0.03	100.0	0.0	0.0
β-Lactamase+ (359)	≤0.015–0.25	≤0.015	0.03	100.0	0.0	0.0
β-Lactamase− (671)	≤0.015–0.5	≤0.015	0.03	100.0	0.0	0.0
Erythromycin						
All (1,032)	0.06–64	4.0	8.0			
β-Lactamase+ (360)	0.5–32	4.0	8.0			
β-Lactamase− (672)	0.06–64	4.0	8.0			
Azithromycin						
All (1,032)	0.03–16	1.0	2.0	99.7	0.0	0.3

Continued on following page

TABLE 7—*Continued*

Antimicrobial agent and phenotype (no. of isolates)[a]	MIC (μg/ml)			Percent[b]		
	Range	50%	90%	S	I	R
β-Lactamase+ (360)	0.12–16	1.0	2.0	99.7	0.0	0.3
β-Lactamase− (672)	0.03–16	1.0	2.0	99.7	0.0	0.3
Clarithromycin						
All (1,032)	0.03–64	4.0	8.0	91.7	7.1	1.3
β-Lactamase+ (360)	1–32	8.0	16	88.9	9.4	1.7
β-Lactamase− (672)	0.03–64	4.0	8.0	93.2	5.8	1.0
Grepafloxacin						
All (1,031)	≤0.004–0.12	≤0.004	0.008	100.0	0.0	0.0
β-Lactamase+ (359)	≤0.004–0.12	≤0.004	0.008	100.0	0.0	0.0
β-Lactamase− (672)	≤0.004–0.12	≤0.004	0.008	100.0	0.0	0.0
Sparfloxacin						
All (1,029)	≤0.004–0.12	≤0.004	0.008	100.0	0.0	0.0
β-Lactamase+ (359)	≤0.004–0.03	≤0.004	0.008	100.0	0.0	0.0
β-Lactamase− (670)	≤0.004–0.12	≤0.004	0.008	100.0	0.0	0.0
Levofloxacin						
All (1,029)	≤0.004–0.12	0.015	0.03	100.0	0.0	0.0
β-Lactamase+ (359)	≤0.004–0.03	0.015	0.015	100.0	0.0	0.0
β-Lactamase− (670)	≤0.004–0.12	0.015	0.03	100.0	0.0	0.0
Ciprofloxacin						
All (1,032)	≤0.004–1	0.008	0.015	100.0	0.0	0.0
β-Lactamase+ (360)	≤0.004–0.25	0.008	0.015	100.0	0.0	0.0
β-Lactamase− (672)	≤0.004–1	0.008	0.015	100.0	0.0	0.0
Ofloxacin						
All (1,032)	≤0.004–1	0.03	0.03	100.0	0.0	0.0
β-Lactamase+ (360)	0.008–0.5	0.03	0.03	100.0	0.0	0.0
β-Lactamase− (672)	≤0.004–1	0.03	0.03	100.0	0.0	0.0
Rifampin						
All (1,029)	≤0.015–>16	0.25	0.25	99.9	0.0	0.1
β-Lactamase+ (359)	≤0.015–>16	0.25	0.25	99.7	0.0	0.3
β-Lactamase− (670)	≤0.015–1	0.25	0.25	100.0	0.0	0.0
Tetracycline						
All (1,032)	≤0.5–>4	≤0.5	≤0.5	98.9	0.3	0.8
β-Lactamase+ (360)	≤0.5–>4	≤0.5	≤0.5	98.1	0.3	1.7
β-Lactamase− (672)	≤0.5–>4	≤0.5	≤0.5	99.4	0.3	0.3
SXT						
All (1,032)	<0.125–>4	≤0.125	4.0	87.5	2.3	10.2
β-Lactamase+ (360)	<0.125–>4	≤0.125	>4	82.5	1.7	15.8
β-Lactamase− (672)	<0.125–>4	≤0.125	0.5	90.2	2.7	7.1

[a] β-Lactamase+, β-lactamase positive; β-Lactamase−, β-lactamase negative.
[b] Percent susceptible (S), intermediate (I), and resistant (R) according to NCCLS breakpoints.
[c] Ampicillin breakpoints were used for amoxicillin.
[d] No NCCLS breakpoints for this antimicrobial agent.

was slightly lower than that (95.3%) reported by Doern et al. (8). The prevalence of clindamycin resistance has remained low and relatively stable, which demonstrates that the M phenotype (susceptibility to clindamycin but resistance to macrolides, indicating the efflux mechanism) currently predominates in the United States (15). Conversely, the level of susceptibility to SXT in our study (88.1%) was much higher than that (74.4%) in the study by Doern and coworkers (8). The in vitro activities of rifampin and vancomycin were consistent with those in a previous report of a study with 1997 isolates (8).

Among the newer antimicrobial agents, the fluoroquinolone class has undergone significant development in recent years. Originally, these antibiotics were not viewed as ideal choices for empiric therapy for respiratory tract infections due to their limited utility against gram-positive organisms, particularly *S. pneumoniae*. However, several newer fluoroquinolones with improved activity against gram-positive organisms have been developed and have been approved by the U.S. Food and Drug Administration for the treatment of upper and lower respiratory tract infections caused by *S. pneumoniae* (2). Pneumococci treated with the new quinolones, which may be administered orally, have not demonstrated resistance associated with penicillin resistance, and the new quinolones are active, clinically and microbiologically, against most species that cause respiratory tract infections (2, 12). The degree to which fluoroquinolones will become a part of the standard of care for respiratory

TABLE 8. Susceptibility of *M. catarrhalis* to 23 selected antimicrobial agents[a]

Antimicrobial agent and phenotype (no. of isolates)[b]	MIC (μg/ml)		
	Range	50%	90%
Amoxicillin			
All (444)	≤0.06–>32	4.0	16
β-Lactamase+ (416)	≤0.06–>32	4.0	16
β-Lactamase− (28)	≤0.06–0.5	≤0.03	0.25
Amoxicillin-clavulanate			
All (444)	≤0.03–4	0.25	0.25
β-Lactamase+ (416)	≤0.03–4	0.25	0.25
β-Lactamase− (28)	≤0.03–0.5	≤0.03	0.25
Cephalothin			
All (444)	0.12–64	4.0	16
β-Lactamase+ (416)	0.12–64	8.0	16
β-Lactamase− (28)	0.12–8	0.5	4.0
Cefaclor			
All (444)	≤0.03–8	1.0	1.0
β-Lactamase+ (416)	≤0.03–8	1.0	1.0
β-Lactamase− (28)	0.12–2	0.25	2.0
Loracarbef			
All (444)	≤0.015–16	2.0	4.0
β-Lactamase+ (416)	≤0.015–16	2.0	4.0
β-Lactamase− (28)	0.12–2	0.12	2.0
Cefuroxime			
All (444)	≤0.03–8	1.0	2.0
β-Lactamase+ (416)	≤0.03–8	1.0	2.0
β-Lactamase− (28)	≤0.03–2	0.5	2.0
Cefprozil			
All (444)	0.06–32	2.0	8.0
β-Lactamase+ (416)	0.06–32	2.0	8.0
β-Lactamase− (28)	0.12–4	0.5	4.0
Cefpodoxime			
All (444)	0.03–2	0.5	1.0
β-Lactamase+ (416)	0.03–2	1.0	1.0
β-Lactamase− (28)	0.03–0.5	0.12	0.5
Cefixime			
All (444)	≤0.25–<8	≤0.25	0.5
β-Lactamase+ (416)	≤0.25–<8	≤0.25	0.5
β-Lactamase− (28)	≤0.25–1	≤0.25	≤0.25
Ceftibuten			
All (444)	≤0.25–>8	2.0	4.0
β-Lactamase+ (416)	≤0.25–>8	2.0	4.0
β-Lactamase− (28)	≤0.25–4	≤0.25	1.0
Cefotaxime			
All (444)	≤0.015–4	0.5	1.0
β-Lactamase+ (416)	0.06–4	0.5	1.0
β-Lactamase− (28)	≤0.015–1	0.06	0.5
Ceftriaxone			
All (444)	≤0.015–4	0.5	1.0
β-Lactamase+ (416)	≤0.015–4	0.5	1.0
β-Lactamase− (28)	≤0.015–0.5	≤0.015	0.12
Erythromycin			
All (444)	≤0.03–8	0.12	0.12
β-Lactamase+ (416)	≤0.03–8	0.12	0.12
β-Lactamase− (28)	≤0.03–2	0.12	2.0
Azithromycin			
All (444)	≤0.03–>64	0.06	0.12

Continued on following page

TABLE 8—*Continued*

Antimicrobial agent and phenotype (no. of isolates)[b]	MIC (μg/ml)		
	Range	50%	90%
β-Lactamase+ (416)	≤0.03–>64	0.06	0.12
β-Lactamase− (28)	≤0.03–1	0.06	0.25
Clarithromycin			
All (444)	≤0.03–8	0.03	0.06
β-Lactamase+ (416)	≤0.03–8	0.03	0.06
β-Lactamase− (28)	≤0.03–1	0.03	0.5
Grepafloxacin			
All (444)	≤0.004–0.06	0.008	0.015
β-Lactamase+ (416)	≤0.004–0.06	0.008	0.015
β-Lactamase− (28)	≤0.004–0.03	0.008	0.015
Sparfloxacin			
All (444)	≤0.004–0.12	0.015	0.015
β-Lactamase+ (416)	≤0.004–0.12	0.015	0.015
β-Lactamase− (28)	≤0.004–0.03	0.015	0.015
Levofloxacin			
All (444)	≤0.004–1	0.03	0.06
β-Lactamase+ (416)	≤0.004–1	0.03	0.06
β-Lactamase− (28)	0.008–0.06	0.03	0.06
Ciprofloxacin			
All (444)	≤0.004–0.5	0.03	0.03
β-Lactamase+ (416)	≤0.004–0.5	0.03	0.03
β-Lactamase− (28)	≤0.004–0.06	0.03	0.03
Ofloxacin			
All (444)	0.015–1	0.06	0.06
β-Lactamase+ (416)	0.015–1	0.06	0.06
β-Lactamase− (28)	0.015–0.12	0.06	0.06
Rifampin			
All (444)	≤0.015–>16	≤0.015	0.03
β-Lactamase+ (416)	≤0.015–>16	≤0.015	0.03
β-Lactamase− (28)	≤0.015–0.5	≤0.015	0.25
Tetracycline			
All (444)	≤0.5–16	≤0.5	≤0.5
β-Lactamase+ (416)	≤0.5–16	≤0.5	≤0.5
β-Lactamase− (28)	≤0.5–4	≤0.5	≤0.5
SXT			
All (444)	<0.125–>4	0.25	1.0
β-Lactamase+ (416)	<0.125–>4	0.25	1.0
β-Lactamase− (28)	<0.125–1	≤0.125	1.0

[a] There are no NCCLS breakpoints for *M. catarrhalis*.
[b] β-Lactamase+, β-lactamase positive; β-Lactamase−, β-lactamase negative.

tract infections remains to be elucidated, but their role in the therapy of pneumonia has been recognized, particularly in cases in which penicillin-resistant *S. pneumoniae* strains are a factor (2).

This study confirms that the fluoroquinolones continue to maintain a high degree of activity against *S. pneumoniae* (≥99.6% of strains were susceptible) and that resistance to this class of agents is rare in the United States. However, the continued practice of analyzing MIC distributions for fluoroquinolones (Table 3) will enable the detection of subtle but potentially significant changes in susceptibility before interpretive categories are breached or MIC_{90}s shift (22).

Variations in susceptibility to β-lactams, macrolides, and SXT were noted when data were stratified by geographic region (Table 4), specimen source (Table 5), and patient age (Table 6). Although susceptibility data in recent studies are not usually analyzed according to these parameters (3, 4, 8), our findings from evaluations with several agents underscore the differences that can occur and the need to monitor resistance according to these and other parameters.

Unlike penicillin resistance in *S. pneumoniae*, the level of which continues to increase, the incidence of β-lactamase-producing *H. influenzae* and *M. catarrhalis* has changed very little in the last few years (6, 7, 11, 21). β-Lactamase production in *H. influenzae* and *M. catarrhalis* compromises the activities of penicillin and amoxicillin (ampicillin) without substantially affecting the activities of most cephalosporins. The exceptions are cefprozil, cefaclor, and loracarbef, which show decreased activity against β-lactamase-positive strains.

During the 1990s, the prevalence of β-lactamase-producing

H. influenzae strains increased to >30%, and this was associated with a concomitant increase in amoxicillin and ampicillin resistance (6, 7, 11, 21). Almost all isolates in this study were susceptible to tetracycline, but the level of resistance to SXT was 10.2%, which was lower than the level of 16.2% reported by Doern et al. (7) for 1997 isolates. Our study's findings of fluoroquinolone MIC_{50}s and MIC_{90}s of ≤0.03 μg/ml are similar to those reported by others (7, 21).

For *M. catarrhalis*, the MIC_{90}s of amoxicillin-clavulanate, cefuroxime, cefixime, and cefotaxime were equivalent to those reported by Doern et al. (7). Overall, the levels of antimicrobial resistance among *H. influenzae* and *M. catarrhalis* isolates have changed little in recent years, but ongoing surveillance is needed to detect increases in resistance, should they occur.

In conclusion, patterns of antimicrobial resistance among *S. pneumoniae* isolates can vary substantially depending on the penicillin susceptibility phenotype of the organism. In turn, these penicillin susceptibility patterns vary by geographic region, site of infection, and age group of the patient. Therefore, thorough evaluations of antimicrobial activities should be done with an extensive strain collection that can capture these potential variations. In addition, such surveillance of drug activities must include newer agents such as the fluoroquinolones for direct comparison with other agents. For examination of the activities of newer agents to which resistance is rare, MIC distribution data are highly useful for establishing benchmarks of current activity and for demonstrating upward drifts in MICs before interpretive breakpoints are breached. Similarly, even though there appear to be no apparent changes in the resistance phenotypes encountered among *H. influenzae* and *M. catarrhalis* isolates, careful monitoring of trends in the MICs for these organisms should be continued.

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