Antimicrobial Agents and Chemotherapy, Nov. 1990, p. 2075–2080
0066-4804/90/112075-06$02.00/0
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Vol. 34, No. 11

Antimicrobial Resistance among Respiratory Isolates of *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Streptococcus pneumoniae* in the United States

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Received 17 April 1990/Accepted 10 August 1990

A national surveillance study was conducted to determine trends in antimicrobial resistance patterns among three common causes of community-acquired respiratory tract infections. Fifteen participating U.S. medical centers submitted clinically significant isolates of *Haemophilus influenzae*, *Moraxella* (*Branhamella*) *catarrhalis*, and *Streptococcus pneumoniae* to two central laboratories for testing with a group of 12 antimicrobial agents. The majority of isolates were recovered from adult males >50 years old. Overall, 84.1% of 378 *M. catarrhalis* and 16.5% of 564 *H. influenzae* (29.5% of type b strains; 15.0% of non-type b strains) produced β-lactamase and were thus resistant to penicillin, ampicillin, and amoxicillin. Resistance in *H. influenzae* to other agents was 2.1% to tetracycline, 0.7% to trimethoprim-sulfamethoxazole, 1.1% to cefaclor, and 0.2% to cefuroxime and amoxicillin-clavulanate, while the *M. catarrhalis* isolates yielded very low MICs of these latter drugs. As demonstrated in prior studies, erythromycin showed little activity against *H. influenzae*. Of 487 *S. pneumoniae* isolates, 1 (0.2%) was penicillin resistant, while 3.8% were relatively resistant to penicillin, 4.5% were resistant to trimethoprim-sulfamethoxazole, 2.3% were resistant to tetracycline, 1.2% were resistant to chloramphenicol, and 0.2% were resistant to erythromycin. Overall, the lowest resistance rates for these common bacterial respiratory pathogens were noted with amoxicillin-clavulanate, cefuroxime, and cefaclor.

Haemophilus influenzae, *Streptococcus pneumoniae*, and *Moraxella* (*Branhamella*) *catarrhalis* are bacterial agents responsible for a number of upper and lower respiratory tract infections, including otitis media (3, 4, 6, 12), maxillary sinusitis (3, 6, 12, 22), community-acquired pneumonia (6, 11), and in some cases, exacerbations of chronic bronchitis (6, 12, 29). These species may harbor resistance mechanisms which affect several antimicrobial agents commonly used to treat such infections (2, 3, 5, 6, 14, 15, 17, 23, 24, 26, 31). Two prior national surveillance studies have documented antimicrobial resistance rates of *H. influenzae* from a variety of infections and in various age groups in the United States (8, 9). An ongoing surveillance system organized by the Centers for Disease Control has shown resistance of systemic isolates of *S. pneumoniae* to penicillin, erythromycin, and tetracycline during the period 1979 to 1987 (J. Spika, R. Facklam, M. Oxtoby, and B. Plikaytis, Program Abstr. 29th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 1287, 1989). National surveillance studies to determine resistance rates in the United States have not been conducted previously with *M. catarrhalis*.

In the present report we describe in detail the findings of a national surveillance study to determine the rates of antimicrobial resistance of *H. influenzae*, *S. pneumoniae*, and *M. catarrhalis* isolates from respiratory infections during the latter half of 1987 and the first half of 1988. Fifteen U.S. medical centers collaborated in this study by collecting and initially characterizing clinically significant isolates of the three species. Isolates were then forwarded to two central laboratories for detailed characterization, including antimicrobial susceptibility testing, with a battery of 12 antimicrobial agents, 10 of which can be administered orally.

MATERIALS AND METHODS

Bacterial isolates. A maximum of 40 isolates each of *H. influenzae*, *M. catarrhalis*, and *S. pneumoniae* from proven or likely significant respiratory tract infections were collected by 15 collaborating U.S. medical centers. The centers included, in the Northeast, Crouse-Irving Memorial Hospital, Syracuse, N.Y.; Long Island Jewish-Hillside Medical Center, New Hyde Park, N.Y.; and the University of Massachusetts Medical Center, Worcester; in the Southeast, Dekalb General Hospital, Decatur, Ga., and Naples Community Hospital, Naples, Fla.; in the Midwest, Barnes Hospital, St. Louis, Mo.; the Medical College of Wisconsin, Milwaukee; and the University of Chicago Medical Center, Chicago, Ill.; in the Southwest, Good Samaritan Medical Center, Phoenix, Ariz.; the University of Texas Health Center, Tyler; and the University of Texas Health Science Center, San Antonio; in the West, Harborview Medical Center, Seattle, Wash.; the University of California at Irvine Medical Center, Orange; the University of Colorado Health Science Center, Denver; and the VA Medical Center, Portland, Oreg.

The study protocol required the participating laboratories to affirm the clinical relevance of sputum samples by microscopic screening procedures to determine specimen quality. Following identification by the participating laboratories, isolates of the three species were forwarded (along with patient demographic information) to one of two central laboratories for further characterization. *H. influenzae* and *S. pneumoniae* isolates were examined at the University of Texas Health Science Center, while *M. catarrhalis* isolates

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were characterized at the University of Massachusetts Medical Center. Characterization included confirmation of the species identity of each isolate by standard methods (25) and determination of whether the *H. influenzae* isolates belonged to serotype b based on slide agglutination testing.

Antimicrobial agents. The following antimicrobial agents were tested against each isolate: ampicillin, amoxicillin (with *H. influenzae* only), ampicillin-sulbactam, amoxicillin-clavulanate, cefaclor, cefuroxime, cephalexin, cephalothin, penicillin (not with *H. influenzae*), erythromycin, chloramphenicol, tetracycline, and trimethoprim-sulfamethoxazole.

Susceptibility testing of *H. influenzae*. Broth microdilution tests were performed by using *Haemophilus* test medium (21), which consisted of Mueller-Hinton broth base (Difco Laboratories, Detroit, Mich.) supplemented with 15 μg of bovine hematin (Sigma Chemical Co., St. Louis, Mo.) per ml, 15 μg of β-NAD (Sigma) per ml, 5 mg of yeast extract (Scott Laboratories, Fiskeville, R.I.) per ml, and 0.2 IU of thymidine phosphorylase (Burroughs-Wellcome, Research Triangle Park, N.C.) per ml. Antimicrobial agent-containing *Haemophilus* test medium broth was dispensed in volumes of 100 μl per well in plastic 96-well microdilution trays. Inocula were prepared by suspending *H. influenzae* grown for 18 h on enriched chocolate agar in Mueller-Hinton broth to match the turbidity of a 0.5 McFarland standard. This suspension was further diluted to provide a final inoculum density of ca. 5×10^5 CFU/ml in the wells of the trays. MICs were determined following 20 to 24 h of incubation at 35°C in ambient air. *H. influenzae* ATCC 10211, *Escherichia coli* ATCC 25922, *E. coli* ATCC 35218, and *Enterococcus faecalis* ATCC 29212 were used for quality control testing of the *Haemophilus* test medium and the antimicrobial agents tested against the *Haemophilus* isolates.

Susceptibility testing of *S. pneumoniae*. Broth microdilution susceptibility tests were performed by using Mueller-Hinton broth (Difco) with 3% lysed horse blood, as recommended by the National Committee for Clinical Laboratory Standards (NCCLS) (28). Twofold concentration increments of antimicrobial agents in the medium were dispensed in amounts of 100 μl per well in plastic 96-well microdilution trays. A suspension of colonies from a 16- to 18-h blood agar plate culture incubated at 35°C in 5% CO_2 was adjusted to the turbidity of a 0.5 McFarland standard. This suspension was further diluted to achieve a final inoculum of ca. 5×10^5 CFU/ml in the microdilution wells. Following incubation at 35°C for 20 to 24 h in ambient air, MIC endpoints were interpreted in the usual manner. *E. coli* ATCC 25922, *E. coli* 35218, and *E. faecalis* ATCC 29212 were used as quality control organisms for the pneumococcal media and antimicrobial agents.

Susceptibility testing of *M. catarrhalis*. Agar dilution susceptibility tests (7) were performed by using Mueller-Hinton agar (Scott Laboratories), to which twofold concentration increments of each of the antimicrobial agents were added before the medium was poured into round plastic petri plates (100 by 15 mm). Thymidine phosphorylase (0.2 IU/ml) was added to the molten Mueller-Hinton agar for tests involving trimethoprim-sulfamethoxazole. Inocula were prepared by suspending growth from an overnight sheep blood agar plate to match the turbidity of a 0.5 McFarland standard. The inoculum suspensions were further diluted and then applied to the surface of the antimicrobial-containing plates by using a Steers replicator to achieve a final inoculum of ca. 10^4 CFU per spot. MICs were interpreted following incubation for 16 to 20 h at 35°C in ambient air. Three well-characterized laboratory strains of *M. catarrhalis* (two β-lactamase positive and one β-lactamase negative) were used for quality control of the agar dilution tests.

TABLE 1. Age distribution of patients from whom isolates were recovered

Age group	*H. influenzae*		*S. pneumoniae* (no. [%])	*M. catarrhalis*	
	No. (%)	% β-Lactamase positive		No (%)	% β-Lactamase positive
0–5 mo	17 (3)	12	16 (3)	27 (7)	89
6 mo–2 yr	29 (5)	24[a]	30 (6)	23 (6)	100[a]
2–6 yr	26 (5)	27[a]	25 (5)	28 (7)	93[a]
7–20 yr	37 (7)	19	26 (5)	14 (4)	86
21–35 yr	76 (14)	12[a]	83 (17)	27 (7)	70[a]
36–50 yr	68 (12)	25[a]	57 (12)	32 (9)	88
51–65 yr	153 (27)	16	99 (20)	96 (25)	80
66–80 yr	119 (21)	15	113 (23)	94 (25)	85
>80 yr	39 (7)	8[a]	38 (8)	37 (10)	78[a]
Total	564	16.5	487	378	84.1

[a] Indicates statistically significant difference ($P \leq 0.05$ by chi-square test) in prevalence of β-lactamase production.

β-Lactamase tests. Each isolate of *H. influenzae* and *M. catarrhalis* was examined for production of β-lactamase by using a nitrocefin-based disk test (Cefinase; Becton Dickinson Microbiology Systems, Cockeysville, Md.).

Chloramphenicol acetyltransferase tests. Selected isolates of *S. pneumoniae* were examined for production of chloramphenicol acetyltransferase by using a commercial disk test (Remel, Lenexa, Kans.). The method of the manufacturer was modified as described by Matthews et al. (26). Specifically, enzyme induction was performed before the chloramphenicol acetyltransferase tests were performed by growing the strains overnight on a sheep blood agar plate with inclusion of a 30-μg chloramphenicol disk. Growth was then taken from around the chloramphenicol inhibition zone margin to prepare the cell suspension for enzyme testing.

RESULTS

The majority of the bacterial respiratory pathogen isolates included in this study were derived from adults with respiratory tract infections (Table 1). More than 50% of the isolates of all three species were obtained from patients >50 years old. The *H. influenzae* and *S. pneumoniae* isolates were recovered from patients with a similar age distribution (Table 2). Compared with *H. influenzae* and *S. pneumoniae*, there were more *M. catarrhalis* isolates from patients less than 6 months old and fewer isolates from adults aged 16 to 50 years. Male patients generated more than 60% of the isolates of all three species.

The most frequent source from which the three species were recovered was sputum (63.5% of all isolates; Table 2). A total of 19.5% of pneumococcal isolates were recovered from the blood of patients with bacteremic pneumonia. Relatively few isolates (<5%) of any of the three species studied were recovered from maxillary sinus aspirates or middle ear fluids.

Overall, 84.1% of the 378 *M. catarrhalis* and 16.5% of the 564 *H. influenzae* isolates produced β-lactamase (Table 2). β-Lactamase production by both species was lowest among patients from 21 to 35 years and >80 years of age (Table 1). The highest prevalence of β-lactamase-producing isolates of both species was documented in those from 6 months to 2 years and 2 to 6 years of age, although the rate of β-lacta-

TABLE 2. Specimen sources of study isolates

Specimen	No. of isolates (% β-lactamase positive)		
	H. influenzae[a]	*S. pneumoniae*	*M. catarrhalis*
Sputum	399 (14)[b]	275	233 (82)
Naso/endotracheal aspirate	69 (22)[b]	38	76 (88)
Bronchoscopy/trans tracheal aspirate	29 (17)	20	14 (92)
Conjuctival exudate	17 (12)	20	19 (100)[b]
Middle ear fluid	6 (0)	18	4 (25)
Sinus aspirate	6 (50)	2	4 (100)
Nasal aspirate	2 (0)	6	17 (88)
Blood	23 (39)[b]	95	3 (67)
Other	13 (8)	13	8 (88)
Total	564 (16.5)	487	378 (84.1)

[a] A total of 58 (10.3%) isolates were serotype b; the specimen sources included sputum (n = 29), blood (n = 20), naso/endotracheal aspirate (n = 5), bronchoscopy/trans tracheal aspirate (n = 4), other or not specified (n = 4).

[b] Indicates statistically significant ($P \leq 0.05$ by chi-square test) difference in prevalence of β-lactamase production.

mase-producing isolates of *H. influenzae* in those from 36 to 50 years of age was also significantly greater than the mean rate of all β-lactamase-producing isolates. Only 10.3% of the *Haemophilus* respiratory isolates represented encapsulated, serotype b strains. Fifty percent of the type b strains were isolated from sputum and 35% were isolated from blood. β-Lactamase production was more common among the type b isolates (29.3%) than among the non-type b strains (15.0%). β-Lactamase production among *H. influenzae* isolates was more frequent among female patients (23% of isolates) than it was among male patients (16%) (P = 0.048; Fisher exact test).

Table 3 relates the antimicrobial susceptibilities of the β-lactamase-positive and -negative *Haemophilus* isolates to the 12 drugs included in the study. Ampicillin and amoxicillin demonstrated essentially equivalent activities against the non-enzyme-producing strains. If analyzed collectively without respect to β-lactamase production and using the current NCCLS interpretive criteria (28) for susceptible, intermediate, and resistant categories, overall rates of resistance were 16.5% to ampicillin, 2.1% to tetracycline, 0.7% to trimethoprim-sulfamethoxazole, 1.1% to cefaclor, and <0.2% to amoxicillin-clavulanate and cefuroxime. Erythromycin showed only marginal activity against the *H. influenzae* strains (Table 3). No chloramphenicol-resistant strains were recovered during this study. Likewise, there were no isolates which were resistant to ampicillin (MIC, ≥4 μg/ml) but which did not produce β-lactamase. However, there were four strains (0.7%) which were β-lactamase negative, for which an intermediate ampicillin MIC of 2 μg/ml was observed, and for which cephalosporin MICs were 8- to 16-fold higher than those for the other β-lactamase-negative strains.

Penicillin resistance (i.e., MIC, 2 μg/ml) was encountered in only a single *S. pneumoniae* strain (0.2%) isolated from a naso/endotracheal sample from a 10-year-old boy. In addition to penicillin, that isolate was resistant to chloramphenicol, tetracycline, and trimethoprim-sulfamethoxazole. Cephalosporin MICs were also substantially elevated for that strain, e.g., cephalexin, 256 μg/ml; cefaclor, 128 μg/ml; and cefuroxime, 4 μg/ml. Relative resistance to penicillin (MICs, 0.12 to 1 μg/ml) was documented in 3.8% of all pneumococcal isolates, while overall resistance (using NCCLS interpretive criteria [28]) to trimethoprim-sulfamethoxazole was 4.5%, resistance to tetracycline was 2.3%, resistance to chloramphenicol was 1.2% (because of chloramphenicol acetyltransferase production), and resistance to erythromycin was 0.2% (Table 4). The majority (63%) of the relatively penicillin-resistant isolates were recovered from sputum, and only two strains were recovered from blood. Two strains were relatively resistant to penicillin and were also resistant to chloramphenicol, tetracycline, and trimethoprim-sulfamethoxazole. In addition, there were eight strains that were relatively resistant to penicillin and resistant to trimethoprim-sulfamethoxazole; one strain that was resistant to chloramphenicol, tetracycline, and trimethoprim-sulfamethoxazole; and two strains that were resistant to both chloramphenicol and tetracycline. There was not a predominant source of isolation of these multiply resistant strains.

With the notable exception of penicillin, ampicillin, and amoxicillin resistance due to β-lactamase production in

TABLE 3. Antimicrobial susceptibilities of 564 *H. influenzae* isolates

Drug	β-Lactamase-positive isolates					β-Lactamase-negative isolates				
	MIC (μg/ml)[a]			% Susceptible	Susceptibility breakpoint (μg/ml)[b]	MIC (μg/ml)[a]			% Susceptible	Susceptibility breakpoint (μg/ml)[b]
	50%	90%	Range			50%	90%	Range		
Ampicillin	16	>16	0.5->16	1	1	0.25	0.5	≤0.125-2	99	1
Amoxicillin	>16	>16	0.5->16			0.5	0.5	≤0.125-4		
Amox-clav[c]	0.5	1	0.25-2	100	4	0.5	0.5	≤0.125-4	100	4
Amp-sulb[d]	1	2	0.25-4	98	2	0.25	0.5	≤0.125-2	100	2
Cephalothin	2	4	≤0.25-8			1	4	≤0.25->32		
Cephalexin	8	16	≤1->32			8	16	≤1->32		
Cefaclor	2	8	≤0.5-32	96	8	2	4	≤0.5->32	99	8
Cefuroxime	1	1	0.25-2	100	4	1	1	≤0.12-16	99	4
Chloramphenicol	0.5	1	≤0.25-2	100	2	0.5	1	≤0.25-2	100	2
Tetracycline	0.5	1	0.25->16	98	2	0.5	1	0.125->16	98	2
Trim-sulfa[e]	0.06	0.12	≤0.008->4	98	0.5	0.06	0.12	≤0.008->4	99	0.5
Erythromycin	8	8	≤0.25->8			8	8	≤0.25->8		

[a] 50% and 90%, MICs for 50 and 90% of strains tested, respectively.

[b] Based on NCCLS interpretive guidelines (25).

[c] Amox-clav, Amoxicillin-clavulanate, 2:1 ratio; numbers indicate amoxicillin component.

[d] Amp-sulb, Ampicillin-sulbactam, 2:1 ratio; numbers indicate ampicillin component.

[e] Trim-sulfa, Trimethoprim-sulfamethoxazole, 1:19 ratio; numbers indicate trimethoprim component.

TABLE 4. Antimicrobial susceptibilities of 486 *S. pneumoniae* isolates

Drug	Penicillin susceptible					Relatively penicillin resistant				
	MIC (μg/ml)[a]			% Susceptible	Susceptibility breakpoint (μg/ml)[b]	MIC (μg/ml)[a]			% Susceptible	Susceptibility breakpoint (μg/ml)[b]
	50%	90%	Range			50%	90%	Range		
Penicillin	0.03	0.03	≤0.015–0.06	100	0.06	0.12	0.25	0.12–0.25	0	0.06
Ampicillin	0.03	0.03	≤0.015–0.25			0.12	0.25	0.06–0.5		
Amox-clav[c]	≤0.015	0.03	≤0.015–0.12			0.06	0.12	0.03–0.25		
Amp-sulb[d]	0.03	0.03	≤0.015–0.25			0.12	0.5	0.06–0.5		
Cephalexin	2	4	≤0.5–8			8	8	4–32		
Cefaclor	0.5	1	≤0.25–2			1	2	0.5–4		
Cefuroxime	0.03	0.03	≤0.015–2			0.25	0.25	0.12–1		
Chloramphenicol	2	4	≤0.5–16	99	4	2	4	2–32	90	4
Tetracycline	≤0.5	≤0.5	≤0.5–128	98	4	≤0.5	≤0.5	≤0.5–64	90	4
Trim-sulfa[e]	0.12	0.5	≤0.03–32	94	0.5	0.12	4	0.06–16	58	0.5
Erythromycin	≤0.5	≤0.5	≤0.5–8	99	0.5	≤0.5	≤0.5	≤0.5	100	0.5

[a] 50% and 90%, MICs for 50 and 90% of strains tested, respectively.
[b] Based on NCCLS interpetive guidelines (25).
[c] Amox-clav, Amoxicillin-clavulanate, 2:1 ratio; numbers indicate amoxicillin component.
[d] Amp-sulb, Ampicillin-sulbactam, 2:1 ratio; numbers indicate ampicillin component.
[e] Trim-sulfa, Trimethoprim-sulfamethoxazole, 1:19 ratio; numbers indicate trimethoprim component.

84.1% of the 378 isolates, MICs of the study drug for the *M. catarrhalis* isolates were uniformly low (Table 5). For β-lactamase-producing strains, MICs of cephalosporins and the β-lactamase inhibitor combinations were from 2- to 16-fold higher than those for the enzyme-negative strains, although specific guidelines for interpretation of *M. catarrhalis* MICs have not been described by NCCLS.

DISCUSSION

This study represented an attempt to determine national trends in antimicrobial resistance patterns of three common bacterial pathogens involved in respiratory tract infections. The majority of isolates characterized in this study were recovered from sputum samples from male patients over age 50. Additional samples from upper respiratory sources such as maxillary sinus or middle ear effusions would have been desirable, although such samples are not often received in most clinical microbiology laboratories.

TABLE 5. Antimicrobial susceptibilities of 378 *M. catarrhalis* isolates

Drugs	MIC (μg/ml)[a]					
	β-Lactamase-positive isolates			β-Lactamase-negative isolates		
	50%	90%	Range	50%	90%	Range
Penicillin	1	8	0.007–16	0.015	0.06	0.007–0.5
Ampicillin	0.12	2	0.007–16	0.007	0.007	0.007–0.12
Amoxicillin	0.25	2	0.007–8	0.007	0.015	0.007–0.25
Amox-clav[b]	0.03	0.25	0.007–0.5	0.007	0.015	0.007–0.25
Amp-sulb[c]	0.03	0.12	0.007–0.25	0.007	0.015	0.007–0.12
Cephalothin	2	4	0.007–16	0.5	1	0.007–1
Cephalexin	2	4	0.007–8	1	2	0.007–4
Cefaclor	0.5	1	0.007–8	0.12	0.25	0.007–0.5
Cefuroxime	0.5	1	0.007–2	0.25	0.5	0.007–1
Tetracycline	0.25	0.5	0.007–1	0.25	0.5	0.007–1
Erythromycin	0.12	0.25	0.007–2	0.12	0.25	0.007–0.25
Trim-sulfa[d]	0.12	0.5	0.007–2	0.06	0.5	0.007–2

[a] 50% and 90%, MICs for 50 and 90% of strains tested, respectively.
[b] Amox-clav, Amoxicillin-clavulanate, 2:1 ratio; numbers indicate amoxicillin component.
[c] Amp-sulb, Ampicillin-sulbactam, 2:1 ratio; numbers, indicate ampicillin component.
[d] Trim-sulfa, Trimethoprim-sulfamethoxazole, 1:19 ratio; numbers indicate trimethoprim component.

The *H. influenzae* resistance rates documented in this study are quite similar to the results of a large, national surveillance study conducted in the United States in 1986 (9), in which *H. influenzae* isolates from a variety of infection sites were studied for antimicrobial resistance properties. In particular, the 15.0% rate of β-lactamase production among non-type b strains in the present study was almost identical to the rate among similar strains in the previous study (9), i.e., 15.6%. While there were relatively fewer type b strains in the current study, the prevalence of strains that produced β-lactamase in this study was also quite similar to that in the aforementioned investigation (9), i.e., 29.3 and 31.7%, respectively. Very similar overall rates of resistance were noted in the two studies (in which identical testing methods were used) with respect to tetracycline (2.0 versus 2.1%, respectively), trimethoprim-sulfamethoxazole (0.7% in both studies), and cefaclor (1.8 versus 1.1%, respectively). The infrequency of cefaclor resistance in this study and the previous study (9) is in contrast to the high rate of resistance (e.g., 60%) reported in two prior multicenter studies (18, 19). This is perhaps due to the fact that cefaclor MICs are often twofold higher when tested in lysed horse blood supplemented Mueller-Hinton broth (as used by Jones and colleagues [18, 19]) than in *Haemophilus* test medium (21), and perhaps is also due in part to the documented instability of cefaclor in culture medium (20). These differences may also be a reflection of the relative lability of cefaclor to the TEM-1 β-lactamase of *H. influenzae* (19) which may result in elevated MICs at increased inoculum concentrations.

None of the 564 *Haemophilus* isolates in the present study were chloramphenicol resistant. However, only 14 such strains (0.5%) were detected in the earlier study (9). The results of this study also confirm the impression that ampicillin-resistant, β-lactamase-negative strains are exceedingly rare (9). However, there were four strains for which the ampicillin MIC was 2 μg/ml (intermediate) and for which cephalosporin MICs were 8- to 16-fold higher than those for the other β-lactamase-negative strains, suggesting the presence of modified or low-affinity penicillin-binding proteins (27).

The rate of relative resistance to penicillin (MICs, 0.125 to 1 μg/ml) among pneumococci in this study was somewhat lower than previous studies in the United States have suggested (range, 6.9 to 15.5%) (13–16, 30). However, the 3.8% prevalence of such strains in our study was virtually identical to that recently reported by the Centers for Disease Control for systemic isolates recovered in 1987 (Spika et al., 29th ICAAC). Penicillin resistance (MIC, ≥2 μg/ml) was exceedingly rare in the present study; i.e., it was found in only a single strain. The MICs of the cephalosporins included in our study were somewhat elevated with the relatively penicillin-resistant strains (Table 4) and substantially elevated in the lone penicillin-resistant strain. Resistance to trimethoprim-sulfamethoxazole and tetracycline was more common in our study than chloramphenicol resistance was. In fact, the 4.5% resistance to trimethoprim-sulfamethoxazole represented the highest rate of pneumococcal resistance among the antimicrobial agents included in this study. However, even higher rates of resistance to this drug combination have been reported in two previous reports (5 to 11.5%) (13, 31).

The 84.1% prevalence of β-lactamase-producing *M. catarrhalis* demonstrated during this national surveillance study is entirely consistent with previous estimates (3, 6) based on local surveys. This high rate of β-lactamase production supports the notion that *M. catarrhalis* should be considered as predictably resistant to penicillin and ampicillin-amoxicillin. Results of this study also support the concept that, in the United States, *M. catarrhalis* is universally susceptible to a wide array of antimicrobial agents which might be chosen for therapy of respiratory infections (1, 7, 10). Although Brown and colleagues (2) recently reported one erythromycin-resistant and two tetracycline-resistant strains based on MIC testing, our findings support the recommendation of NCCLS (28) that, at present, only β-lactamase determinations are necessary in the routine testing of *M. catarrhalis* for susceptibility to antimicrobial agents.

In summary, the antimicrobial agents which showed the best overall in vitro activity against the three common community-acquired bacterial respiratory tract pathogens that we tested were amoxicillin-clavulanate, cefuroxime, cefaclor, chloramphenicol, and to a lesser degree, tetracycline. Resistance was problematic among the other drugs because of differences among species in their susceptibilities to specific agents, e.g., penicillin, ampicillin, and amoxicillin resistance because of β-lactamase production in *M. catarrhalis* and *H. influenzae* (and relative resistance in *S. pneumoniae*), poor erythromycin activity against *H. influenzae*, and trimethoprim-sulfamethoxazole resistance among pneumococci.

ACKNOWLEDGMENTS

We thank the following individuals for providing the study isolates: Marie Coyle (Harborview Medical Center), Silas Farmer (Medical College of Wisconsin), Paul Granato (Crouse-Irving Memorial Hospital), Henry Isenberg (Long Island Jewish-Hillside Medical Center), Robert Jerris (Dekalb General Hospital), Patrick Murray (Barnes Hospital), Mark Neuman (Naples Community Hospital), Marie Pezzlo (University of California at Irvine Medical Center), Barth Reller (University of Colorado Health Science Center), Daniel Sahm (University of Chicago Medical Center), David Sewell (Veterans Administration Medical Center), Michael Saubolle (Good Samaritan Medical Center), and Richard Wallace (University of Texas Health Center). We thank Thomas Prihoda and Yolan Marinez for data base maintenance and statistical analysis. Critical review of the manuscript by Jeffrey Collins is gratefully acknowledged.

This study was supported in part by a grant from Glaxo, Inc., Research Triangle Park, N.C.

LITERATURE CITED

1. **Ahmad, F., D. T. McLeod, M. J. Croughan, and M. A. Calder.** 1984. Antimicrobial susceptibility of *Branhamella catarrhalis* isolates from bronchopulmonary infections. Antimicrob. Agents Chemother. **26:**424–425.
2. **Brown, B. A., R. J. Wallace, Jr., C. W. Flanagan, R. W. Wilson, J. I. Luman, and S. D. Redditt.** 1989. Tetracycline and erythromycin resistance among clinical isolates of *Branhamella catarrhalis*. Antimicrob. Agents Chemother. **33:**1631–1633.
3. **Calder, M. A., M. J. Croughan, D. T. McLeod, and F. Ahmad.** 1986. The incidence and antibiotic susceptibility of *Branhamella catarrhalis* in respiratory infections. Drugs **31:**11–16.
4. **Calhoun, R. H., W. B. Norris, J. A. Hokanson, C. M. Stiernberg, and F. B. Quinn.** 1988. Bacteriology of middle ear effusions. South. Med. J. **81:**332–336.
5. **Dang-Van, A., G. Tiraby, J. F. Acar, W. V. Shaw, and D. H. Bouanchaud.** 1978. Chloramphenicol resistance in *Streptococcus pneumoniae*: enzymatic acetylation and possible plasmid linkage. Antimicrob. Agents Chemother. **13:**577–583.
6. **Doern, G. V.** 1986. *Branhamella catarrhalis*: an emerging human pathogen. Diagn. Microbiol. Infect. Dis. **4:**191–201.
7. **Doern, G. V., and R. N. Jones.** 1988. Antimicrobial susceptibility testing of *Haemophilus influenzae*, *Branhamella catarrhalis*, and *Neisseria gonorrhoeae*. Antimicrob. Agents Chemother. **32:**1747–1753.
8. **Doern, G. V., J. H. Jorgensen, C. Thornsberry, D. A. Preston, and the *Haemophilus influenzae* Surveillance Group.** 1986. Prevalence of antimicrobial resistance among clinical associates of *Haemophilus influenzae*: a collaborative study. Diagn. Microbiol. Infect. Dis. **4:**95–107.
9. **Doern, G. V., J. H. Jorgensen, C. Thornsberry, D. A. Preston, T. Tubert, J. S. Redding, and L. A. Maher.** 1988. National collaborative study of the prevalence of antimicrobial resistance among clinical isolates of *Haemophilus influenzae*. Antimicrob. Agents Chemother. **32:**180–185.
10. **Doern, G. V., and T. A. Tubert.** 1988. In vitro activities of 39 antimicrobial agents for *Branhamella catarrhalis* and comparison of results with different quantitative susceptibility test methods. Antimicrob. Agents Chemother. **32:**259–261.
11. **Donowitz, G. R., and G. L. Mandell.** 1985. Acute pneumonia, p. 394–404. *In* G. L. Mandell, R. G. Douglas, Jr., and J. E. Bennett (ed.), Principles and practice of infectious diseases, 2nd ed. John Wiley & Sons, Inc., New York.
12. **Hager, H., A. Verghese, S. Alvarez, and S. L. Berk.** 1987. *Branhamella catarrhalis* respiratory infections. Rev. Infect. Dis. **9:**1140–1149.
13. **Henderson, F. W., P. H. Gilligan, K. Wait, and D. A. Goff.** 1988. Nasopharyngeal carriage of antibiotic-resistant pneumococci by children in group day care. J. Infect. Dis. **157:**256–263.
14. **Istre, G. R., J. T. Humphreys, K. D. Albrecht, C. Thornsberry, J. M. Swenson, and R. S. Hopkins.** 1983. Chloramphenicol and penicillin resistance in pneumococci isolated from blood and cerebrospinal fluid: a prevalence study in metropolitan Denver. J. Clin. Microbiol. **17:**472–475.
15. **Istre, G. R., M. Tarpay, M. Anderson, A. Pryor, and D. Welch.** 1987. Invasive disease due to *Streptococcus pneumoniae* in an area with a high rate of relative penicillin resistance. J. Infect. Dis. **156:**732–735.
16. **Jackson, M. A., S. Shelton, J. D. Nelson, and G. H. McCracken.** 1984. Relatively penicillin-resistant pneumococcal infections in pediatric patients. Pediatr. Infect. Dis. **3:**129–132.
17. **Jacobs, M. R., H. J. Koornhof, R. M. Robins-Browne, C. M. Stevenson, Z. A. Vermaak, I. Freiman, G. B. Miller, M. A. Whitcomb, M. Isaacson, J. I. Ward, and R. Austrian.** 1978. Emergence of multiply resistant pneumococci. N. Engl. J. Med. **299:**735–740.
18. **Jones, R. N., and A. L. Barry.** 1988. Antimicrobial activity, spectrum, and recommendations for disk diffusion susceptibility

testing of ceftibuten (7432-S; SCH 39720), a new orally administered cephalosporin. Antimicrob. Agents Chemother. **32:** 1576–1582.

19. **Jones, R. N., A. L. Barry, and the Collaborative Antimicrobial Testing Group.** 1988. BMY-28100, a new oral cephalosporin: antimicrobial activity against nearly 7,000 recent clinical isolates, comparative potency with other oral agents, and activity against beta-lactamase producing isolates. Diagn. Microbiol. Infect. Dis. **91:**11–26.
20. **Jorgensen, J. H., J. S. Redding, and L. A. Maher.** 1988. Influence of storage and susceptibility test conditions on stability and activity of LY163892 and four other cephalosporins. Antimicrob. Agents Chemother. **32:**1477–1480.
21. **Jorgensen, J. H., J. S. Redding, L. A. Maher, and A. W. Howell.** 1987. Improved medium for antimicrobial susceptibility testing of *Haemophilus influenzae*. J. Clin. Microbiol. **25:**2105–2113.
22. **Jousimies-Somer, H. R., S. Savolainen, and J. S. Ylikoski.** 1988. Bacteriologic findings of acute maxillary sinusitis in young adults. J. Clin. Microbiol. **26:**1919–1925.
23. **Klugman, K. P., and H. J. Koornhof.** 1988. Drug resistance patterns and serogroups or serotypes of pneumococcal isolates from cerebrospinal fluid or blood, 1979–1986. J. Infect. Dis. **158:**956–964.
24. **Latorre, C., T. Juncosa, and I. Sanfeliu.** 1985. Antibiotic resistance and serotypes of 100 *Streptococcus pneumoniae* strains isolated in a children's hospital in Barcelona, Spain. Antimicrob. Agents Chemother. **28:**357–359.
25. **Lennette, E. H., A. Balows, W. J. Hausler, Jr., and H. J. Shadomy (ed.).** 1985. Manual of clinical microbiology, 4th ed. American Society for Microbiology, Washington, D.C.
26. **Matthews, H. W., C. N. Baker, and C. Thornsberry.** 1988. Relationship between in vitro susceptibility test results for chloramphenicol and production of chloramphenicol acetyltransferase by *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Aerococcus* species. J. Clin. Microbiol. **26:**2387–2390.
27. **Mendelman, P. M., D. O. Chaffin, T. L. Stull, C. E. Rubens, K. D. Mack, and A. L. Smith.** 1984. Characterization of non-β-lactamase-mediated ampicillin resistance in *Haemophilus influenzae*. Antimicrob. Agents Chemother. **26:**235–244.
28. **National Committee for Clinical Laboratory Standards.** 1988. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. Tentative standard M7-T2. National Committee for Clinical Laboratory Standards, Villanova, Pa.
29. **Reynolds, H. Y.** 1985. Chronic bronchitis and acute infectious exacerbations, p. 387–390. *In* G. L. Mandell, R. G. Douglas, Jr., and J. E. Bennett (ed.), Principles and practice of infectious diseases, 2nd ed. John Wiley & Sons, Inc., New York.
30. **Saah, A. J., J. P. Mallonee, M. M. Tarpay, C. Thornsberry, M. A. Roberts, and E. R. Rhodes.** 1980. Relative resistance to penicillin in the pneumococcus. A prevalence and case-controlled study. J. Am. Med. Assoc. **243:**1824–1827.
31. **Tarpay, M. M., D. F. Welch, H. Salari, and M. I. Marks.** 1982. In vitro activity of antibiotics commonly used in the treatment of otitis media against *Streptococcus pneumoniae* isolates with different susceptibilities to penicillin. Antimicrob. Agents Chemother. **22:**145–147.