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Haemophilus influenzae and *Moraxella catarrhalis* from Patients with Community-Acquired Respiratory Tract Infections: Antimicrobial Susceptibility Patterns from the SENTRY Antimicrobial Surveillance Program (United States and Canada, 1997)

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Between February and June of 1997, a large number of community-acquired respiratory tract isolates of *Haemophilus influenzae* (n = 1,077) and *Moraxella catarrhalis* (n = 503) from 27 U.S. and 7 Canadian medical centers were characterized as part of the SENTRY Antimicrobial Surveillance Program. Overall prevalences of β-lactamase production were 33.5% in *H. influenzae* and 92.2% in *M. catarrhalis* with no differences noted between isolates recovered in the United States and those from Canada. Among a total of 21 different antimicrobial agents tested, including six cephalosporins, a β-lactamase inhibitor combination, three macrolides, tetracycline, trimethoprim-sulfamethoxazole (TMP-SMX), rifampin, chloramphenicol, five fluoroquinolones, and quinupristin-dalfopristin, resistance rates of >5% with *H. influenzae* were observed only with cefaclor (12.8%) and TMP-SMX (16.2%).

The empiric management of community-acquired respiratory tract infections such as otitis media, sinusitis, acute purulent exacerbation of chronic bronchitis, and community-acquired pneumonia has been complicated by the emergence of high rates of antimicrobial resistance in three major pathogens: *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. Of these, only *S. pneumoniae* has been the focus of numerous recent studies, perhaps because of its greater virulence and the fact that antimicrobial resistance in this pneumococcus has reached extraordinary levels over a very short period in North America (1, 2, 7, 12, 26). However, *H. influenzae* and *M. catarrhalis* remain a problem in the context of antimicrobial resistance.

At least 11 systematic, nationwide surveillance studies of antimicrobial resistance in *H. influenzae* have been conducted in North America during the past 15 years, eight in the United States (2, 6, 9, 10, 17, 18, 23, 30) and three in Canada (24, 25, 27). The earliest of these studies, performed from 1983 to 1984, characterized 3,356 clinical isolates of *H. influenzae* from 22 U.S. medical centers and revealed an overall prevalence of β-lactamase-mediated ampicillin resistance of 15.2% (9). The two most recent studies, both conducted in the United States from 1994 to 1995, revealed overall rates of β-lactamase production of 35.6% among 1,605 isolates from 30 centers and 36.1% among 2,278 strains from 187 institutions (6, 17). In general, the prevalences of β-lactamase-producing isolates of *H. influenzae* in the United States and Canada have been roughly comparable. Resistance to other antimicrobial agents such as the cephalosporins, β-lactamase inhibitor combinations, macrolides, tetracycline, chloramphenicol, trimethoprim-sulfamethoxazole (TMP-SMX), and the fluoroquinolones has remained relatively uncommon with *H. influenzae* in North America (2, 6, 17, 30).

β-Lactamase-mediated resistance to penicillins in *M. catarrhalis* is even more common than in *H. influenzae*. Four large, multicenter, national surveillance studies conducted in the United States during the 1990s revealed an overall rate of β-lactamase production in *M. catarrhalis* of between 90.1 and 96.8% (2, 8, 18, 30). Resistance to other antimicrobials has not emerged as a significant problem with this organism.

The question arises: what is the current prevalence of antimicrobial resistance in respiratory tract isolates of *H. influenzae* and *M. catarrhalis* in North America? In an attempt to answer this question, a 5-month, multicenter surveillance study was performed in the United States and Canada during 1997. This investigation was conducted as part of the SENTRY Antimicrobial Surveillance Program, a prospective, longitudinal, multinational study aimed at tracking the emergence of antimicrobial resistance worldwide.

During the 5-month period from February through June 1997, a total of 837 isolates of *H. influenzae* and 374 isolates of *M. catarrhalis* were recovered in the clinical microbiology laboratories of 27 medical centers in the United States (Table 1). A total of 240 isolates of *H. influenzae* and 129 isolates of *M. catarrhalis* were recovered in the laboratories of seven Canadian hospitals during the same period (Table 1). All isolates were transported to the coordinating laboratory, the University of Iowa College of Medicine (Iowa City), where stock cultures were prepared in defibrinated rabbit blood and frozen at −70°C. Only organisms judged to be the cause of defined respiratory tract infections in outpatients were included in this study. Criteria in place at individual laboratories were used to assess clinical significance. Frozen isolates were thawed and subcultured twice on 5% sheep blood agar plates prior to further characterization.

At the coordinating study center, the identity of isolates was confirmed by using conventional criteria (4, 20) and the MICs

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TABLE 1. β-Lactamase-mediated ampicillin resistance among respiratory tract isolates of *H. influenzae* and *M. catarrhalis* from U.S. and Canadian medical centers

Country	Site	*H. influenzae*		*M. catarrhalis*	
		No. of isolates	% β-Lactamase positive	No. of isolates	% β-Lactamase positive
United States	Veterans Administration Medical Center, Boston, Mass.	35	20.0	18	88.9
	Columbia Presbyterian Medical Center, New York, N.Y.	37	29.7	15	93.3
	Long Island Jewish Medical Center, New Hyde Park, N.Y.	31	25.8	7	100.0
	Strong Memorial Hospital, Rochester, N.Y.	39	43.6	19	89.5
	The Medical Center of Delaware, Wilmington	32	43.8	19	84.2
	University of Virginia Health Sciences Center, Charlottesville	16	37.5	5	100.0
	Carolinas Medical Center, Charlotte, N.C.	40	37.5	19	89.5
	University Medical Center, Jacksonville, Fla.	37	27.0	20	85.0
	University of Mississippi Medical Center, Jackson	21	38.1	9	100.0
	University of Louisville Hospital, Louisville, Ky.	33	30.3	20	95.0
	Summa Health Systems, Akron, Ohio	37	32.4	6	66.7
	Henry Ford Hospital, Detroit, Mich.	38	47.4	15	93.3
	Methodist Hospital of Indiana, Indianapolis	39	23.1	16	87.5
	Northwestern Memorial Hospital, Chicago, Ill.	15	33.3	4	100.0
	University of Illinois Hospital, Chicago	22	50.0	10	90.0
	Froedtert Memorial Lutheran Hospital, Milwaukee, Wis.	40	37.5	10	70.0
	Barnes-Jewish Hospital, St. Louis, Mo.	21	23.8	10	80.0
	University of Iowa Hospitals and Clinics, Iowa City	35	48.6	20	100.0
	Creighton University Medical Center, Omaha, Nebr.	37	29.7	18	88.9
	Parkland Health & Hospital System, Dallas, Tex.	9	11.1	7	85.7
	University of Texas Medical Branch at Galveston, Galveston	24	33.3	21	100.0
	Denver General Hospital, Denver, Colo.	29	34.5	4	66.7
	University of New Mexico Hospital, Albuquerque	39	38.5	10	100.0
	St. Jude Medical Center, Fullerton, Calif.	36	30.6	11	100.0
	Kaiser Regional Laboratory, Berkeley, Calif.	31	35.5	17	100.0
	Sacred Heart Medical Center, Spokane, Wash.	33	18.2	21	95.2
	University of Washington, Seattle	25	48.0	10	100.0
	Subtotal (United States)	837	34.2	374	92.0
Canada	Queen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia	39	48.7	21	85.7
	Royal Victoria Hospital, Montreal, Quebec	34	23.5	16	75.0
	Ottawa General Hospital, Ottawa, Ontario	38	21.1	20	100.0
	Mount Sinai Hospital, Toronto, Ontario	19	26.3	20	100.0
	The Hospital for Sick Children, Toronto, Ontario	37	37.8	17	100.0
	Health Sciences Centre, Winnipeg, Manitoba	35	28.6	23	95.7
	University of Alberta Hospital Site, Edmonton	38	28.9	12	91.7
	Subtotal (Canada)	240	31.3	129	93.0
	Grand total	1,077	33.5	503	92.2

of 21 antimicrobial agents were determined by a reference broth microdilution method (21). The following antimicrobials were tested: amoxicillin, amoxicillin-clavulanate, cefaclor, cefuroxime, cefixime, cefpodoxime, cefotaxime, cefepime, azithromycin, clarithromycin, erythromycin, chloramphenicol, tetracycline, TMP-SMX, rifampin, ciprofloxacin, levofloxacin, gatifloxacin, sparfloxacin, trovafloxacin, and quinupristin-dalfopristin. Dehydrated microdilution trays were obtained commercially (Dade-MicroScan, Inc., Sacramento, Calif.). Drugs were tested over concentration ranges that yielded on-scale MICs with >98% of organism-antimicrobial combinations. Haemophilus test medium broth, 100 μl per well, was employed as a growth medium for *H. influenzae* during MIC determinations (11, 19, 21). Cation-adjusted Mueller-Hinton broth, 100 μl per well, was used in MIC determinations for *M. catarrhalis* (21). The final inoculum concentration was approximately 5×10^5 CFU/ml. Trays were incubated for 20 to 24 h at 35°C in ambient air prior to MIC determinations. MICs were defined as the lowest concentration of drug that yielded no visible evidence of growth of the test organism. *H. influenzae* ATCC 49247 and ATCC 49766 were used as control organisms throughout this study. Production of β-lactamase was assessed by use of the Cefinase disk test (Becton Dickinson Microbiology Systems, Cockeysville, Md.).

A total of 1,077 isolates of *H. influenzae* were characterized, 837 from 27 U.S. medical centers and 240 from seven Canadian institutions (Table 1). The overall prevalences of β-lactamase-producing strains were 34.2% in the United States and 31.3% in Canada ($P = 0.09$). Collectively in North America, 33.5% of respiratory tract isolates of *H. influenzae* produced β-lactamase. Among centers with at least 20 isolates, rates of β-lactamase production varied between 18.2 and 50.0% (Table 1).

Results of MIC determinations with 14 selected antimicrobial agents against this collection of *H. influenzae* are summarized in Table 2. Isolates from U.S. and Canadian medical centers were grouped together for purposes of this analysis because when they were analyzed separately, no significant differences were noted between the two countries (data not shown). Among β-lactam agents, resistance was not detected with cefixime (MIC at which 90% of the isolates are inhibited [MIC_{90}], 0.12 μg/ml), cefpodoxime (MIC_{90}, 0.25 μg/ml), cefo-

TABLE 2. In vitro activities of 14 antimicrobial agents against 1,077 respiratory tract isolates of *H. influenzae* from North American medical centers

Antimicrobial agent	MIC (μg/ml)				% by category[a]		Breakpoint[a]	
	50%	90%	Range	Mode	Susceptible	Resistant	Susceptible	Resistant
Amoxicillin-clavulanate	0.5	2	≤0.06–16	0.25–2	99.8	0.2	≤4/2	≥8/4
Cefaclor	2	32	≤0.25–>32	2	79.6	12.8	≤8	≥32
Cefuroxime	0.5	2	≤0.06–16	0.5	95.7	1.5	≤4	≥16
Cefixime	≤0.03	0.12	≤0.03–1	≤0.03	100.0		≤1	
Cefpodoxime	0.06	0.25	≤0.03–1	0.06	100.0		≤2	
Cefotaxime	0.015	0.06	≤0.008–0.5	0.015	100.0		≤2	
Cefepime	0.12	0.25	≤0.06–2	0.12	100.0		≤2	
Azithromycin	2	2	≤0.12–>16	2	99.8	0.2	≤4	
Clarithromycin	8	16	≤0.25–>32	8	61.4	3.9	≤8	≥32
Erythromycin	4	8	≤0.25–>32	4				
Chloramphenicol	≤2	≤2	≤2–>16	≤2	99.0	0.7	≤2	≥8
Tetracycline	≤2	≤2	≤2–>16	≤2	98.6	0.9	≤2	≥8
TMP-SMX	≤0.25	8	≤0.25–>8	≤0.25	77.3	16.2	≤0.5	≥4
Rifampin	≤1	≤1	≤1–>2	≤1	95.7	0.1	≤1	≥4

[a] Breakpoints are those advocated by the NCCLS for use in MIC determinations with *H. influenzae* (17).

taxime (MIC_{90}, 0.06 μg/ml), and cefepime (MIC_{90}, 0.25 μg/ml). Resistance was uncommon with amoxicillin-clavulanate (0.2% of isolates) and cefuroxime (1.5%). Resistance among β-lactams was most common with cefaclor (12.8%). Resistance was also uncommon with selected non-β-lactam antimicrobial agents, i.e., azithromycin (0.2%), clarithromycin (3.9%), chloramphenicol (0.7%), tetracycline (0.9%), and rifampin (0.1%). In contrast, 16.2% of *H. influenzae* isolates were resistant to TMP-SMX.

Among the five fluoroquinolones examined in this study, i.e., ciprofloxacin, levofloxacin, sparfloxacin, trovafloxacin, and gatifloxacin, a nearly uniform activity was observed for study strains of *H. influenzae* for which the MIC_{50}s, MIC_{90}s, and modal MICs were ≤0.06 μg/ml. The highest MIC obtained with any of these agents was 0.25 μg/ml (data not shown). The combination quinupristin-dalfopristin was characterized by a MIC_{50}, MIC_{90}, and modal MIC of 4, 8, and 4 μg/ml, respectively.

Amoxicillin MICs for all of the 361 β-lactamase-producing isolates in this study were ≥4 μg/ml; for only 1 of 716 β-lactamase-negative isolates (i.e., 0.1%) was the amoxicillin MIC 8 μg/ml, indicating resistance. The amoxicillin-clavulanate MIC for this isolate was 8/4 μg/ml. Two β-lactamase-positive isolates of *H. influenzae* (i.e., 0.2%) that were resistant to amoxicillin-clavulanate (MICs of ≥8/4 μg/ml) were recovered in this study. The amoxicillin-clavulanate MICs for these two strains were confirmed by repeat testing. Other than amoxicillin, of the antimicrobial agents examined in this study, only cefaclor activity appeared to be adversely influenced by β-lactamase-production in *H. influenzae*. The following cefaclor MICs were obtained with β-lactamase-positive and -negative strains, respectively: MIC_{50}s, 8 and 2 μg/ml; MIC_{90}s, >32 and 8 μg/ml; modal MICs, 8 and 2 μg/ml; susceptibility rates, 54.0 and 92.5%; and resistance rates, 32.7 and 2.5%. Essentially comparable in vitro activity was noted with all other agents when the results obtained with these agents were compared with β-lactamase-positive and β-lactamase-negative strains (data not shown).

A total of 503 isolates of *M. catarrhalis* were characterized in this study, 374 from the United States and 129 from Canada (Table 1). The overall prevalence of β-lactamase production was 92.2% and very uniform between the two countries, i.e., 92.0% in the United States and 93.0% in Canada. MICs are

TABLE 3. In vitro activities of 14 antimicrobial agents against 503 respiratory tract isolates of *M. catarrhalis* from North American medical centers

Antimicrobial agent	MIC (μg/ml)				% by category[a]		Breakpoint[a]	
	50%	90%	Range	Mode	Susceptible	Resistant	Susceptible	Resistant
Amoxicillin-clavulanate	0.12	0.25	≤0.06–4	0.25	100.0	0.0	≤8/4	≥16/8
Cefaclor	1	2	≤0.25–32	0.50	99.6	0.2	≤8	≥32
Cefuroxime	1	2	0.12–8	1	99.2	0.0	≤4	≥32
Cefixime	0.25	0.5	≤0.03–2	0.25	99.4	0.0	≤1	≥4
Cefpodoxime	1	2	≤0.03–>4	1	99.0	0.2	≤2	≥8
Cefotaxime	0.5	1	≤0.008–2	0.5	100.0	0.0	≤8	≥64
Cefepime	1	4	≤0.06–8	1	100.0	0.0	≤8	≥32
Azithromycin	≤0.12	≤0.12	≤0.12–0.25	≤0.12	100.0	0.0	≤2	≥8
Clarithromycin	≤0.25	≤0.25	≤0.25–1	≤0.25	100.0	0.0	≤2	≥8
Erythromycin	≤0.25	0.5	≤0.25–1	≤0.25	99.0	0.0	≤0.5	≥8
Chloramphenicol	≤2	≤2	≤2	≤2	100.0	0.0	≤8	≥32
Tetracycline	≤2	≤2	≤2	≤2	100.0	0.0	≤4	≥16
TMP-SMX	≤0.25	0.5	≤0.25–8	≤0.25	99.2	0.2	≤2/38	≥8/152
Rifampin	≤1	≤1	≤1	≤1	100.0	0.0	≤1	≥4

[a] Breakpoints are those advocated by the NCCLS for use in MIC determinations with nonfastidious bacteria that grow well on unsupplemented Mueller-Hinton medium (17).

listed for 14 selected antimicrobial agents in Table 3. All of these compounds were consistently active against this collection of *M. catarrhalis* isolates. In addition, the five fluoroquinolones examined in this study were uniformly active against *M. catarrhalis* at very low concentrations. The MIC_{90}s of these agents were as follows: ciprofloxacin, ≤0.03 μg/ml; levofloxacin, ≤0.05; gatifloxacin, ≤0.03 μg/ml; sparfloxacin, ≤0.12 μg/ml; and trovafloxacin, ≤0.03 μg/ml. The highest MICs obtained with each of these fluoroquinolones were 1, 2, 1, 0.5, and 0.5 μg/ml, respectively (data not shown). The MIC_{50} and MIC_{90} of quinupristin-dalfopristin were both 0.5 μg/ml (range, ≤0.06 to >8 μg/ml).

Amoxicillin MICs for the 464 β-lactamase-producing isolates of *M. catarrhalis* in this study varied substantially (range, ≤0.06 to >8 μg/ml). The number of β-lactamase-positive isolates for which amoxicillin MICs were ≤1, 2, 4, and ≥8 μg/ml were 103 (22.2%), 61 (13.1%), 89 (19.2%), and 211 (45.5%), respectively. By contrast, amoxicillin-clavulanate MICs were ≤1 μg/ml for all 464 β-lactamase-positive isolates.

The results of this survey indicate that the prevalence of β-lactamase production among respiratory tract isolates of *H. influenzae* (i.e., 33.5%) may have leveled off in North America. Two recent multicenter U.S. surveillance studies which emphasized respiratory tract isolates of *H. influenzae*, both conducted in 1994 to 1995, revealed overall rates of β-lactamase production of 35.6 and 36.1% (6, 11). As has been observed in previous studies (6, 17, 24, 25, 27), only small differences were noted in the current investigation between the rates of β-lactamase production in the United States (34.2%) and Canada (31.3%). Amoxicillin resistance among β-lactamase-negative strains and amoxicillin-clavulanate resistance among β-lactamase-positive strains, as has been described recently (6), were uncommon in the current survey (i.e., 0.1 and 0.2%, respectively).

Among the 19 other antimicrobial agents examined in this study, only two compounds were characterized by resistance rates greater than 5% in *H. influenzae*, cefaclor (12.8%) and TMP-SMX (16.2%). With cefaclor, much higher resistance rates were noted in β-lactamase-producing isolates than in organisms that lacked β-lactamase production. The actual clinical implications of these findings remain to be defined. Several recent studies have questioned the clinical predictive value of MICs obtained with oral antimicrobial agents used to treat localized respiratory tract infections caused by *H. influenzae* (5, 15, 16).

The results of this study corroborate the findings of previous investigators regarding the high prevalence of β-lactamase production among respiratory tract isolates of *M. catarrhalis* (2, 8, 18, 30). Overall, 92.2% of 503 isolates produced β-lactamase, 92.0% in the United States and 93.0% in Canada. Amoxicillin MICs were ≤1 μg/ml for 22.2% of β-lactamase-producing isolates, which probably would be considered to indicate susceptibility. Similar observations have been made previously with *M. catarrhalis* and may reflect the fact that some β-lactamase-positive strains produce a BRO-2 enzyme (3, 28, 29). This enzyme is produced in small amounts, remains tightly cell associated, and has a low affinity for aminopenicillins such as ampicillin and amoxicillin. Ampicillin and amoxicillin MICs for BRO-2-producing strains of *M. catarrhalis* are typically found to be low (3, 28) and represent one example of where production of a β-lactamase does not actually result in ampicillin-amoxicillin resistance. All β-lactamase-producing strains of *M. catarrhalis* were inhibited by concentrations of ≤4/2 μg of amoxicillin-clavulanate per ml.

The 19 remaining antimicrobial agents examined in this investigation were almost uniformly active against *M. catarrhalis* (Table 3). The activities of these agents were assessed based on breakpoints advocated by the National Committee for Clinical Laboratory Standards (NCCLS) for use in testing nonfastidious bacteria that grow well on unsupplemented Mueller-Hinton medium, as is the case with *M. catarrhalis* (13). Two previous studies demonstrated that such breakpoints were applicable to *M. catarrhalis* (13, 14). Based on these breakpoints, resistance was observed with only three compounds (cefaclor, cefotaxime, and TMP-SMX) and then only with a single isolate each.

In conclusion, in this multicenter, North American surveillance study, 33.5 and 92.2% of community-acquired respiratory tract isolates of *H. influenzae* and *M. catarrhalis*, respectively, were found to produce β-lactamase. As a result of β-lactamase production, amoxicillin resistance with these two organisms is common. In contrast, with the exception of cefaclor and TMP-SMX tested against *H. influenzae*, all of the alternative antimicrobials examined in this investigation were nearly uniformly active against both organisms. Because of the longitudinal nature of the SENTRY Antimicrobial Surveillance Program, we will continue to track the susceptibility trends of both *H. influenzae* and *M. catarrhalis* in North America over the next several years.

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