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Decreasing Prevalence of β-Lactamase Production among Respiratory Tract Isolates of *Haemophilus influenzae* in the United States

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A total of 986 isolates of *Haemophilus influenzae* from patients with respiratory tract infections in 45 United States medical centers were characterized during the winter of 2002–2003. β-Lactamase production was noted with 26.2% of isolates; 14.6% were resistant to trimethoprim-sulfamethoxazole. Resistance to other relevant antimicrobial agents was extremely uncommon. In comparison to the results of four previous national surveys conducted since 1994, the prevalence of β-lactamase production with this pathogen appears to be decreasing.

Haemophilus influenzae is a common respiratory tract pathogen often implicated as a cause of acute otitis media, bacterial rhinosinusitis, acute exacerbation of chronic bronchitis, and community-acquired pneumonia. Resistance to ampicillin was first described in 1974 (18). The mechanism of ampicillin resistance in *H. influenzae* is production of either a TEM-1 or ROB-1 beta-lactamase (10). The prevalence of beta-lactamase-mediated ampicillin resistance steadily increased during the decade of the 1980s (15), reaching levels of 35 to 40% by the mid-1990s (3, 4, 6, 14). More recent studies have raised the question, are rates of beta-lactamase production decreasing (5, 7–9, 11–13, 16, 17, 22, 24, 25)? Beta-lactamase-negative ampicillin-resistant strains (BLNAR) were first described in 1980 (19); beta-lactamase-positive amoxicillin-clavulanate-resistant strains have also been reported (5–7, 22). Both phenotypes remain rare.

Resistance to chloramphenicol and tetracycline continues to occur infrequently, while resistance rates to trimethoprim-sulfamethoxazole (TMP-SMX) has steadily risen. One study conducted in 2000–2001 reported a rate of TMP-SMX resistance of 18% (16). Fluoroquinolone resistance remains uncommon with *H. influenzae*. The first reported isolate was in 1993, with a ciprofloxacin MIC of 8 μg/ml (1). Using a ciprofloxacin MIC of ≥0.12 μg/ml to define reduced susceptibility, a 5-year study conducted between 1997 and 2001 found an overall rate of 0.15% reduced ciprofloxacin susceptibility among 11,355 isolates (2). Only two isolates in this study had ciprofloxacin MICs of ≥1 μg/ml.

In this investigation, we examined the prevalence of beta-lactamase production and the rates of resistance for 16 antimicrobial agents versus a large collection of respiratory tract isolates of *H. influenzae* (n = 986) obtained from different patients in 45 United States medical centers between 1 November 2002 and 30 April 2003. The results of this survey are compared to results obtained during four previous studies conducted since 1994. The 45 medical centers that participated in this survey are listed in the Acknowledgments section. The number of isolates submitted by each center varied between 4 and 29 (mean = 22). Only isolates judged to be of clinical significance by the referring center were included. The following patient demographic information was supplied with each isolate: age, sex, in patient versus out patient, specimen source, and date of isolation. Organisms were sent to the University of Iowa, where their identity was confirmed as *H. influenzae* by standard methods and stock cultures prepared using the Microbank bead system (ProLab Diagnostics, Ontario, Canada) with subsequent storage at −80°C.

MICs were determined by broth microdilution as outlined by the NCCLS using Haemophilus Test Medium (20). MIC trays were prepared in house and frozen at −80°C. The following drugs were examined: ampicillin, amoxicillin-clavulanate, cefidinir, cefpodoxime, cefprozil, cefuroxime, ceftriaxone, clarithromycin, azithromycin, ciprofloxacin, levofloxacin, moxifloxacin, TMP-SMX, chloramphenicol, tetracycline, and telithromycin. Quality control was accomplished using *Haemophilus influenzae* ATCC 49247 and ATCC 49766. Beta-lactamase testing was performed using the Nitrocefin disk assay (Becton Dickinson Company, Sparks, Md.). Rates of resistance were determined using NCCLS MIC interpretive criteria (21). P values were calculated by the Chi-squared method.

Among 986 isolates from 2002–2003, the overall rate of β-lactamase production was 26.2%. When sorted according to different patient demographic factors (Table 1), highest rates were noted among isolates of *H. influenzae* from females, patients between the ages of 6 to 20 years old, and organisms recovered from sinus aspirates and from outpatients. The prevalence of β-lactamase production was found to vary only slightly when examined based on geographic region of the country, with the highest rate noted in the east north central region (i.e., 37.2%) and the lowest rate in the Pacific region (i.e., 19.4%).

The in vitro activity and resistance rates obtained with 16 antimicrobial agents versus this collection of *H. influenzae* are presented in Table 2. Only ampicillin and TMP-SMX were problematic in terms of resistance with overall resistance rates of 26% and 14.6%, respectively. Resistance rates with other

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TABLE 1. Rates of beta-lactamase production sorted according to patient demographics (2002–2003)

Criterion	Total no. (%) of isolates	% Positive
Gender		
Male	595 (60.3)	24.7
Female	389 (39.4)	28.0
Unknown	2 (0.3)	100.0
Age		
0–5	227 (23)	31.7
6–20	107 (10.9)	32.7
21–64	430 (43.6)	22.3
≥65	221 (22.4)	25.0
Unknown	1 (0.1)	0.0
Specimen source		
Lower respiratory tract	704 (71.4)	24.1
Upper respiratory tract	47 (4.8)	31.9
Eye	62 (6.2)	24.1
Ear	62 (6.2)	27.4
Sinus	58 (5.9)	48.3
Blood	36 (3.7)	22.2
CSF/BF[a]	6 (0.7)	33.3
Other	11 (1.1)	27.3
Patient Status		
Inpatient	608 (61.7)	25.0
Outpatient	365 (37)	28.4
Unknown	13 (1.3)	15.4

[a] CSF/BF, cerebrospinal fluid and other normally sterile body fluids.

agents varied between 0 and 1.7%. With the exception of ampicillin, resistance rates obtained with β-lactamase-negative isolates were generally similar to those obtained with β-lactamase-positive organisms, although in the cases of cefdinir, cefprozil, cefuroxime, chloramphenicol, and tetracycline, statistically significantly larger numbers of isolates in the latter category were found to be either intermediate or resistant. Among the 728 β-lactamase negative isolates, 3.3% were ampicillin nonsusceptible (3.2% intermediate; 0.1% resistant) (BLNAR). All of these isolates were susceptible to amoxicillin-clavulanate. Among the 258 β-lactamase-positive strains, 0.4% were amoxicillin-clavulanate resistant (BLPACR).

It is evident from the results of this survey, in which the in vitro activity of various antimicrobial agents was assessed versus respiratory tract isolates of *H. influenzae* from across the United States, that resistance continues to be a problem with ampicillin/amoxicillin and TMP-SMX. In contrast, resistance was found to be uncommon with numerous other antimicrobial agents commonly used to treat respiratory tract infections. These included the advanced generation macrolides, azithromycin and clarithromycin, amoxicillin-clavulanate, expanded spectrum generation oral cephalosporins, tetracyclines, respiratory fluoroquinolones, and the recently introduced ketolide agent, telithromycin.

Resistance rates obtained in the current study were compared to the results of four previous survey conducted since 1994 (Table 3). The same isolate inclusion criteria and test methods were used in all studies as was the period of isolate collection (i.e., November 1 to April 30). Twenty-two centers participated in all five surveys; 32 participated in four of five

TABLE 2. In vitro activity of 16 antimicrobial agents for 986 clinical isolates of *Haemophilus influenzae* (2002–2003)

Antimicrobial agent	All isolates (n = 986)[a]						β-Lactamase-negative isolates (n = 728)						β-Lactamase-positive isolates (n = 258)					
	MIC_{50}	MIC_{90}	Range	%S	%I	%R	MIC_{50}	MIC_{90}	Range	%S	%I	%R	MIC_{50}	MIC_{90}	Range	%S	%I	%R
Ampicillin	0.25	32	≤0.06–>128	71.4	2.3	26.3	0.25	1	≤0.06–8	96.7	3.2	0.1	32	>128	4–>128			100
Amoxicillin-clavulanate	0.5	1	≤0.06–8	99.9		0.1	0.5	1	≤0.06–4	100			1	2	0.12–8	99.6		0.4
Cefdinir	0.25	0.5	≤0.008–2	99.4			0.25	1	≤0.008–2	99.7		0.3	0.25	0.5	≤0.008–2	98.5		1.5
Cefpodoxime	0.06	0.12	≤0.008–2	100			0.06	0.25	≤0.008–2	100			0.06	0.12	≤0.008–2	100		
Cefprozil	2	4	≤0.12–64	95.5	3.7	0.8	2	4	≤0.12–32	96.8	2.9	0.3	2	8	≤0.12–64	91.9	5.8	2.3
Cefuroxime	1	2	≤0.12–32	99.6	0.3	0.1	1	2	≤0.12–8	99.7	0.3		0.5	2	≤0.12–32	99.2	0.4	0.4
Ceftriaxone	≤0.015	≤0.015	≤0.015–0.5	100			≤0.015	≤0.015	≤0.015–0.5	100			≤0.015	≤0.015	≤0.015–0.12	100		
Ciprofloxacin	≤0.015	≤0.015	≤0.015–0.06	100			≤0.015	≤0.015	≤0.015–0.06	100			≤0.015	≤0.015	≤0.015–0.03	100		
Levofloxacin	0.03	0.03	≤0.008–0.06	100			0.03	0.03	≤0.008–0.06	100			0.03	0.03	≤0.008–0.06	100		
Moxifloxacin	0.03	0.06	≤0.008–0.25	100			0.03	0.06	≤0.008–0.25	100			0.03	0.06	≤0.008–0.06	100		
Clarithromycin	8	16	≤0.12–128	82	16.3	1.7	8	16	0.25–128	82.8	15.3	1.9	8	16	≤0.12–128	79.5	19.4	1.2
Azithromycin	1	2	≤0.12–32	99			1	2	≤0.12–32	98.9			1	2	≤0.12–8	99.2		
Trimethoprim-sulfamethoxazole	0.12	8	≤0.015–32	82.3	3.1	14.6	0.12	4	≤0.015–32	82.1	3.4	14.4	0.06	8	≤0.015–16	82.6	2.3	15.1
Chloramphenicol	0.5	0.5	≤0.015–16	99.4	0.2	0.4	0.5	0.5	≤0.015–2	100			0.5	0.5	≤0.015–16	98.5	1.2	0.4
Tetracycline	0.5	0.5	≤0.12–32	99.1	0.5	0.4	0.5	0.5	≤0.12–32	99.6	0.1	0.3	0.5	0.5	≤0.12–16	97.7	1.6	0.8
Telithromycin	2	4	.06–16	98.1	1.6	0.3	2	4	0.06–16	97.9	1.8	0.3	2	4	0.06–16	98.5	1.2	0.4

[a] %S, percent susceptible; %I, percent intermediate; %R, percent resistant.

TABLE 3. Comparison of resistant rates with *Haemophilus influenzae* during five study periods between 1994–1995 and 2002–2003

Antimicrobial agent or resistance factor	Percentage resistant in				
	1994–1995[a]	1997–1998[b]	1999–2000[c]	2000–2001[d]	2002–2003[e]
β-Lactamase positive	36.4	31.1	30.8	28.9	26.2
BLNAR[f]	1.3	1.9	2.0	0.7	0.1
BLPACR[g]	3.0	2.0	0.2	0.7	0.4
Ampicillin	36.6	32.4	34.6	29.4	26.3
Amoxicillin-clavulanate	5.0	2.4	0.3	0.5	0.1
Cefprodoxime	0.1	0.0	0.1	0.1	0.0
Cefuroxime	1.5	1.0	1.1	0.5	0.1
Clarithromycin	1.8	4.2	6.8	6.3	1.7
Azithromycin	0.5	1.9	2.9	2.4	1.0
TMP-SMX	9.0	18.3	14.6	17.6	14.6
Chloramphenicol	0.5	0.5	0.5	0.6	0.4
Tetracycline	1.3	1.0	0.7	1.1	0.4

[a] 1537 isolates from 34 centers (5)
[b] 1529 isolates from 34 centers (data on file)
[c] 1354 isolates from 33 centers (data on file)
[d] 1025 isolates from 45 centers (data on file)
[e] 986 isolates from 45 centers (current study)
[f] BLNAR, percentage of β-lactamase negative isolates that were resistant to ampicillin.
[g] BLPACR, percentage of β-lactamase positive isolates that were resistant to amoxicillin-clavulanate.

surveys. The proportion of isolates from patients in different age groups and genders and from different specimens was roughly comparable in all five surveys. The results of our 1994–1995 survey have been described previously in the literature (5). The results of our 1997–1998, 1999–2000, and 2000–2001 surveys are data on file.

As depicted in Table 3, there appears to have been a steady decline in prevalence of β-lactamase production during the past decade in the United States. This downward trend was statistically significant (P value <0.05). These findings are consistent with the observations of various point prevalence surveillance studies conducted sporadically during this period (5, 7–9, 11–13, 16, 17, 22, 24, 25). Importantly, strains with either the BLNAR and BLPACR phenotypes remain uncommon.

It is possible to speculate on the cause for the apparent decreasing prevalence of β-lactamase production with *H. influenzae*. During the decade of the 1990s there has been a shift away from using amoxicillin and less potent oral cephalosporins such as cefaclor, loracarbef, and cefprozil in the treatment of community-acquired respiratory tract infections toward use of amoxicillin/clavulanate, macrolides, more potent advanced generation oral cephalosporins, and fluoroquinolones. It is possible that this changing paradigm has resulted in less pressure for selection of β-lactamase-producing strains of *H. influenzae*.

It is reassuring to note that, not withstanding increased use of fluoroquinolones in the treatment of community-acquired respiratory tract infections in adults in the United States, a profile that began to change in 1997 with the introduction of levofloxacin, fluoroquinolone resistance has not yet developed as a problem with *H. influenzae*. In our survey, no isolates were found to be resistant to ciprofloxacin, levofloxacin, or moxifloxacin. This observation is consistent with the results of at least one previously published study (23). Further, we have observed no trend towards increasing fluoroquinolone MICs during the past decade.

In the broadest sense, these observations suggest that antibiotic cycling, even in the community setting, might represent one approach to dealing with the problem of resistance. It is also reassuring that antimicrobial resistance, at least with *H. influenzae*, appears to be a soluble problem.

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REFERENCES

1. **Barriere, S. L., and J. A. Hindler.** 1993. Ciprofloxacin-resistant Haemophilus influenzae infection in a patient with chronic lung disease. Ann. Pharmacother. **27:**309–310.
2. **Biedenbach, D. J., and R. N. Jones.** 2003. Five-year analysis of Haemophilus influenzae isolates with reduced susceptibility to flouroquinolones: prevalence results from the SENTRY antimicrobial surveillance program. Diagn. Microbiol. Infect. Dis. **46:**55–61.
3. **Derecola, A., D. L. Butler, R. L. Kaplan, L. A. Miller, and J. A. Poupard.** 1999. A 5-year surveillance study of 44,691 isolates of *Haemophilus influenzae* project Beta-Alert 1993–1997. Antimicrob. Agents Chemother. **43:**185–186.
4. **Doern, G. V.** 1996. Antimicrobial resistance among lower respiratory tract isolates of Haemophilus influenzae: results of a 1992–93 western Europe and USA collaborative surveillance study. The Alexander Project Collaborative Group. J. Antimicrob. Chemother. **38:**59–69.
5. **Doern, G. V., and S. D. Brown.** 2004. Antimicrobial susceptibility among community-acquired respiratory tract pathogens in the USA: data from PROTEKT US 2000–01. J. Infect. **48:**56–65.
6. **Doern, G. V., A. B. Brueggemann, G. Pierce, H. P. Holley, Jr., and A. Rauch.** 1997. Antibiotic resistance among clinical isolates of *Haemophilus influenzae* in the United States in 1994 and 1995 and detection of beta-lactamase-positive strains resistant to amoxicillin-clavulanate: results of a national multicenter surveillance study. Antimicrob. Agents Chemother. **41**:292–297.
7. **Doern, G. V., R. N. Jones, M. A. Pfaller, and K. Kugler.** 1999. *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). Antimicrob. Agents Chemother. **43:**385–389.
8. **Hoban, D. J., and D. Felmingham.** 2002. The PROTEKT surveillance study: antimicrobial susceptibility of Haemophilus influenzae and Moraxella catarrhalis from community-acquired respiratory tract infections. J. Antimicrob. Chemother. **50:**49–59.
9. **Hoban, D. J., K. Waites, and D. Felmingham.** 2003. Antimicrobial susceptibility of community-acquired respiratory tract pathogens in North America in 1999–2000: findings of the PROTEKT surveillance study. Diagn. Microbiol. Infect. Dis. **45:**251–259.
10. **Jacobs, M. R., J. Anon, and P. C. Appelbaum.** 2004. Mechanisms of resistance among respiratory tract pathogens. Clinics Lab. Med. **24:**419–453.
11. **Jacobs, M. R., D. Felmingham, P. C. Appelbaum, R. N. Gruneberg, and T. A. P. Group.** 2003. The Alexander Project 1998–2000: susceptibility of pathogens isolated from community-acquired respiratory tract infection to commonly used antimicrobial agents. J. Antimicrob. Chemother. **52:**229–246.
12. **Johnson, D. M., H. S. Sader, T. R. Fritsche, D. J. Biedenbach, and R. N. Jones.** 2003. Susceptibility trends of Haemophilus influenzae and Moraxella catarrhalis against orally administered antimicrobial agents: five year report from the SENTRY Antimicrobial Surveillance Program. Diagn. Microbiol. Infect. Dis. **47:**373–376.
13. **Jones, M. E., J. A. Karlowsky, R. S. Blosser-Middleton, I. Critchley, C. Thornsberry, and D. F. Sahm.** 2002. Apparent plateau in b-lacatamase production among clinical isolates of Haemophilus influenzae and Moraxella catarrhalis in the United States: results from the LIBRA Surveillance initiative. International J. Antimicrob. Agents **19:**119–123.
14. **Jones, R. N., M. R. Jacobs, J. A. Washington, and M. A. Pfaller.** 1997. A 1994–95 survey of Haemophilus influenzae susceptibility to ten orally administered agents. A 187 clinical laboratory center sample in the United States. Diagn. Microbiol. Infect. Dis. **27:**75–83.
15. **Jorgensen, J. H., G. V. Doern, L. A. Maher, A. Howell, W, and J. S. Redding.** 1990. Antimicrobial resistance among respiratory isolates of *Haemophilus influenzae*, *Moraxella catarrhalis* and *Streptococcus pneumoniae* in the United States. Antimicrob. Agents Chemother. **34**:2075–2080.
16. **Karlowsky, J. A., I. A. Critchley, R. S. Blosser-Middleton, E. A. Karginova, M. E. Jones, C. Thornsberry, and D. F. Sahm.** 2002. Antimicrobial surveillance of *Haemophilus influenzae* in the United States during 2000–2001 leads to detection of clonal dissemination of a beta-lactamase-negative and ampicillin-resistant strain. J. Clin. Microbiol. **40:**1063–1066.
17. **Karlowsky, J. A., D. C. Draghi, C. Thornsberry, M. E. Jones, I. Critchley, and D. F. Sahm.** 2002. Antimicrobial susceptibilities of Streptococcus pneumoniae, Haemophilus influenzae and Moraxella catarrhalis isolates in two successive respiratory seasons in the US. Int. J. Antimicrob. Agents **20:**76–85.
18. **Khan, W., S. Ross, W. Rodriguez, G. Contrini, and A. K. Saz.** 1974. Haemophilus influenzae type B resistant to ampicillin. A report of two cases. JAMA **229:**299–301.
19. **Markowitz, S. M.** 1980. Isolation of an ampicillin-resistant, non-B-lactamase-producing strain of *Haemophilus influenzae*. Antimicrob. Agents Chemother. **17:**80–83.
20. **National Committee for Clinical Laboratory Standards.** 2000. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. Approved standard M7-A5. NCCLS, Wayne, Pa.
21. **National Committee for Clinical Laboratory Standards.** 2004. Performance standards for antimicrobial susceptibility testing. Approved standard M100-S14. NCCLS, Wayne, Pa.
22. **Richter, S. S., A. B. Brueggemann, H. K. Huynh, P. R. Rhomberg, E. M. Wingert, R. Flamm, and G. V. Doern.** 1999. A 1997–1998 national surveillance study: Moraxella catarrhalis and Haemophilus influenzae antimicrobial resistance in 34 US institutions. International J. Antimicrob. Agents **13:**99–107.
23. **Thornsberry, C., P. Ogilvie, J. Kahn, and Y. Mauriz.** 1997. Surveillance of antimicrobial resistance in Streptococcus pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis in the United States in 1996–1997 respiratory season. The Laboratory Investigator Group. Diagn. Microbiol. Infect. Dis. **29:**249–257.
24. **Thornsberry, C., P. T. Ogilvie, H. P. Holley, Jr., and D. F. Sahm.** 1999. Survey of susceptibilities of *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis isolates* to 26 antimicrobial agents: a prospective U.S. study. Antimicrob. Agents Chemother. **43**:2612–2623.
25. **Thornsberry, C., D. F. Sahm, L. J. Kelly, I. Critchley, M. E. Jones, A. T. Evangelista, and J. A. Karlowsky.** 2002. Regional Trends in antimicrobial resistance among clinical isolates of Streptococcus pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis in the United States: results from the TRUST Surveillance Program, 1999–2000. Clin. Infect. Dis. **34:**S4–S16.