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Macrolide Susceptibility and β-Lactamase Production among *Haemophilus influenzae* Isolates in the United States, 1996–1997

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In 1996 and 1997, 68 hospital laboratories throughout the United States determined the β-lactamase production and susceptibility to macrolides of 1,998 isolates of *Haemophilus influenzae* obtained from patients with community-acquired respiratory tract infections. The MICs at which 90% of the isolates are inhibited of azithromycin, erythromycin, and clarithromycin were 4, 8, and 16 μg/ml, respectively. By National Committee for Clinical Laboratory Standards interpretive criteria, 99 and 78% of the isolates were susceptible to azithromycin and clarithromycin, respectively. The prevalence of β-lactamase production was 32%.

Haemophilus influenzae is one of several causes of otitis media, sinusitis, acute exacerbation of chronic bronchitis, and pneumonia. These diseases often are treated empirically with oral antibiotics, and the results of national surveillance studies of antibiotic susceptibility provide a basis for rational therapy. The aim of the present study was to determine the prevalence of β-lactamase production and the macrolide susceptibility of recent isolates of *H. influenzae* in the United States.

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Methods. The MICs of azithromycin, clarithromycin, and erythromycin against consecutive clinical isolates of *H. influenzae* recovered from the sputum of patients with community-acquired respiratory tract infections were determined by 68 hospital laboratories between 1 March 1996 and 31 July 1997. All determinations were performed according to National Committee for Clinical Laboratory Standards (NCCLS) guidelines (5) by the broth dilution method using microtiter trays prepared for the study by PML Microbiologicals (Tualatin, Oreg.). Susceptibility was evaluated on the basis of NCCLS interpretive breakpoints (no breakpoint has been established for erythromycin) (6). β-Lactamase production was determined by a nitrocefin-based filter paper spot test.

Results and discussion. The in vitro activities of the study antibiotics are presented in Table 1. On the basis of weight, azithromycin was more active than erythromycin, and both were more active than clarithromycin. Comparison of the data in Tables 1 and 2 suggests that the in vitro activities of azithromycin and clarithromycin have not changed significantly since they became commercially available in 1992 and 1991, respectively.

There was little variation by region in the percentages of susceptibility to either antibiotic (Table 3), and in all regions, a greater proportion of the *H. influenzae* isolates was susceptible to azithromycin than to clarithromycin. Our results are similar to those of Doern and associates (2), who found the susceptibilities to azithromycin and clarithromycin of 1,537 isolates of *H. influenzae* at 30 centers in 1994 and 1995 to be >99.5 and 71%, respectively. The difference in susceptibility of *H. influenzae* to the two antibiotics is possibly attributable to the presence of an extra positive charge on the azithromycin molecule, which has been reported to en-

TABLE 1. In vitro activities (MICs)[a] of macrolides against isolates of *H. influenzae*, 1996–1997

U.S. region	No. of isolates	Azithromycin			Clarithromycin			Erythromycin		
		MIC_{50}[b]	MIC_{90}	Range	MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}	Range
East	835	1	4	0.03–256	8	16	0.25–256	4	8	0.03–256
Midwest	757	1	4	0.03–32	8	16	0.125–256	4	8	0.25–256
West	406	1	4	0.03–128	8	16	0.03–256	4	8	0.03–128
All regions	1,998	1	4	0.03–256	8	16	0.03–256	4	8	0.03–256

[a] MICs are reported as micrograms per milliliter.
[b] MIC_{50}, the MIC at which 50% of the isolates are inhibited.

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TABLE 2. Published in vitro activities (MICs)[a] of azithromycin and clarithromycin against isolates of *H. influenzae*

Reference	Time of collection	No. of isolates	Azithromycin		Clarithromycin	
			MIC_{50}[b]	MIC_{90}	MIC_{50}	MIC_{90}
Fung-Tomc et al. (4)	1987–1992	135	2	2	8	8
Barry et al. (1)	1992–1993	890	2	2	8	16
Doern et al. (2)	1994–1995	1,537	2	2	8	16

[a] MICs are reported as micrograms per milliliter.
[b] MIC_{50}, the MIC at which 50% of the isolates are inhibited.

TABLE 3. Susceptibility to azithromycin and clarithromycin of isolates of *H. influenzae*, 1996–1997

β-Lactamase status by U.S. region	No. of isolates	No. (%)[a] of azithromycin isolates susceptible[b]	No. (%)[a] of clarithromycin isolates susceptible[b]
East			
Negative	532	528 (99)	416 (78)
Positive	297	294 (99)	209 (70)
Both	829	822 (99)	625 (75)
Midwest			
Negative	523	518 (99)	421 (81)
Positive	233	228 (98)	184 (79)
Both	756	746 (99)	605 (80)
West			
Negative	287	284 (99)	225 (78)
Positive	119	119 (100)	88 (74)
Both	406	403 (99)	313 (77)
All regions			
Negative	1,342	1,330 (99)	1,062 (79)
Positive	649	641 (99)	481 (74)
Both	1,991	1,971 (99)	1,543 (78)

[a] Rounded to the nearest whole number.
[b] Based on NCCLS (2) susceptibility breakpoints for azithromycin and clarithromycin (≤4 and ≤8 μg/ml, respectively).

hance its ability to penetrate the gram-negative bacterial cell wall (3).

Overall, 32% of the *H. influenzae* isolates produced β-lactamase, a prevalence similar to that observed by Doern and colleagues in their 1994 and 1995 isolates (34.6%) (2). In our study, there was little geographic variation in the prevalence of β-lactamase production. In the East (28 hospitals, 835 isolates), 36% of isolates were β-lactamase positive (median, 35%; range, 13–66%). In the Midwest (26 hospitals, 757 isolates), 31% of isolates were β-lactamase positive (median, 30%; range, 7–50%). In the West (14 hospitals; 406 isolates), 29% of isolates were β-lactamase positive (median, 29%; range 7–57%).

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