Susceptibility of *Streptococcus pneumoniae* and *Haemophilus influenzae* in 1997: Results of a Hospital-Based Study

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ABSTRACT

To monitor the current levels of resistance in the United States, a total of 3,334 *Haemophilus influenzae* and 3,241 *Streptococcus pneumoniae* strains isolated from respiratory and blood sources were tested at 47 US hospitals. The E-test method was used to determine MICs. For *S pneumoniae*, 24.9% were penicillin intermediate and 15.1% were penicillin resistant; 34% of *H influenzae* were β-lactamase positive.

This study showed that β-lactam-resistance remains high in both species and that macrolide resistance is increasing in *S pneumoniae*: 26.3% of *S pneumoniae* were resistant to clarithromycin, which includes 6.8% of the penicillin-susceptible and 55.7% of the penicillin-nonsusceptible strains. Among *S pneumoniae*, 30 strains had ciprofloxacin MICs of >8 µg/ml, representing the emergence of quinolone-resistant strains. Amoxicillin/clavulanic acid was the most active oral agent against *S pneumoniae*. Only one β-lactamase–negative ampicillin-resistant *H influenzae* strain was found. Amoxicillin/clavulanic acid, cefixime, and ciprofloxacin were the most active agents against *H influenzae*, with no resistant strains.

Following submission of the abstract, we analyzed additional data, determining major differences in susceptibility in different geographic regions and age groups. The highest rate of β-lactamase production was in the southeast region (36.8%), in patients younger than 2 years (41.8%), and in patients aged 3 to 10 years (37.3%). *S pneumoniae* penicillin resistance (including penicillin-intermediate and -resistant isolates) was highest in the south central (55.3%), followed by the southeast (43.0%). The penicillin resistance rate was nearly 50% in patients younger than 2 years and 45% in patients aged 3 to 10.

INTRODUCTION

- The rate of resistance of *S pneumoniae* to penicillin has increased since it was first reported in 1967
  Penicillin resistance rates (including both intermediate and resistant strains) as high as 35.5% have been reported recently[1]
- Similarly, since β-lactamase production was first reported in 1964, the percentage of strains producing the enzyme has increased
  36% of *H influenzae* isolates tested positive for β-lactamase production in a 1994–1995 study[2]
- In light of the changing antimicrobial resistance of these two important respiratory pathogens and the impact their resistance has on therapy, continuing to monitor their susceptibility patterns is more important than ever

METHODS

Isolates

- From January to December 1997, 3,334 *H influenzae* and 3,241 *S pneumoniae* isolates were collected from respiratory and blood sources (Table 1)

Table 1. Distribution of *S pneumoniae* Isolates by Specimen Source

	H influenzae		*S pneumoniae*	
Source	No. Isolates	Percent	No. Isolates	Percent
Blood	24	0.7	446	13.8
Middle ear	123	3.7	235	7.3
Eye	203	6.1	136	4.2
Nasopharynx	237	7.1	283	8.7
Paranasal sinus	79	2.4	103	3.2
Lower respiratory tract	2466	74.0	1894	58.4
Throat	134	4.0	41	1.3
Other	62	1.9	80	2.5
Unknown	6	0.2	23	0.7

- *S pneumoniae* isolates were identified at participating hospitals based on gram stain, colony morphology, and bile solubility or optochin tests
- *H influenzae* was identified based on gram stain, colony morphology, and XV factor requirement or porphyrin tests
- The 47 participating hospitals, located throughout the United States, were divided into six geographic areas for regional data analysis (Table 2)

Susceptibility Test Methods

- β-Lactamase testing of *H influenzae* strains was performed using the nitrocefin method
- Amoxicillin/clavulanic acid, ampicillin (*H influenzae* only), penicillin (*S pneumoniae* only), cefixime, cefprozil, ciprofloxacin, and clarithromycin MICs were determined by E-test procedures by participating hospitals
- *S pneumoniae* isolates tested using Mueller Hinton with 5% sheep blood agar (Remel, Lenexa, Kansas), and *H influenzae* isolates tested using Hemophilus Test Medium (HTM) (Remel)
  All plates were incubated for 18–24 hours in 5% CO_2 atmosphere
- Quality control organisms were tested once before clinical isolates were tested and subsequently each time clinical isolates were tested
  H influenzae (ATCC 49247)
  H influenzae (ATCC 49766)
  S pneumoniae (ATCC 49619)
  Escherichia coli (ATCC 35218)
- Quality control and patient isolate results were repeated if any quality control values were outside expected limits
- Strains that demonstrated unusual susceptibility patterns were sent to a central laboratory for further testing by NCCLS reference procedures[3]
  These included *H influenzae* isolates resistant to amoxicillin/clavulanic acid, cefixime, and/or ciprofloxacin and *S pneumoniae* isolates with ciprofloxacin MICs ≥8 µg/ml

METHODS (cont'd)

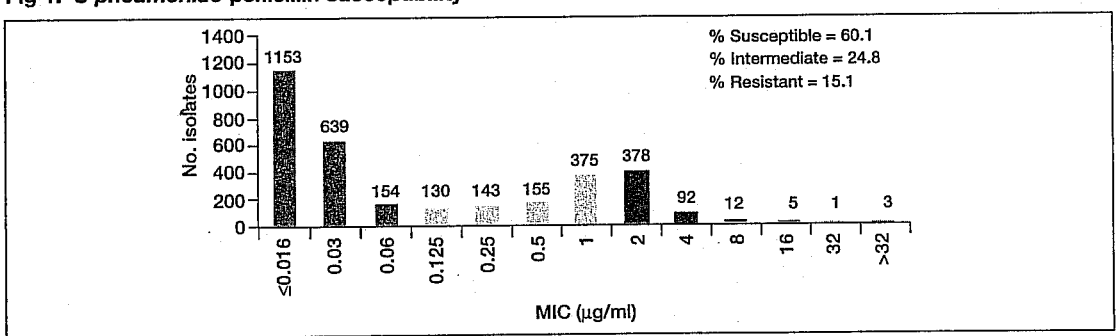
Table 2. Distribution of *S pneumoniae* and *H influenzae* Isolates by US Region

Region	Participating Hospitals	% Strains Submitted	
		S pneumoniae	*H influenzae*
North Central	Rush/Presbyterian St. Luke, Chicago, IL	16.5	16.9
	University of Iowa Hospital and Clinic, Iowa City, IA		
	University of Kansas, Kansas City, KS		
	Cardinal Glennon Children's, St. Louis, MO		
	Creighton University/St. Joseph, Omaha, NB		
	Sioux Valley Hospital, Sioux Falls, SD		
	Medical College of Wisconsin, Milwaukee, WI		
Northeast	Hospital of St. Raphael, New Haven, CT	27.7	24.6
	Clarion Health, Indianapolis, IN		
	University of Maryland Medical System, Baltimore, MD		
	New England Medical Center, Boston, MA		
	University of Michigan, Ann Arbor, MI		
	Dartmouth/Hitchcock, Lebanon, NH		
	Albany Medical Center, Albany, NY		
	New York University Medical Center, New York, NY		
	North Shore University Hospital, Manhasset, NY		
	Grant/Riverside Methodist, Columbus, OH		
	University Hospitals of Cleveland, Cleveland, OH		
	M.S. Hershey Medical Center, Hershey, PA		
	St. Christopher's Hospital, Philadelphia, PA		
Northwest	E. Idaho Regional Medical Center, Idaho Falls, ID	10.0	10.0
	Fairview University Medical Center, Minneapolis, MN		
	Providence St. Vincent Medical Center, Portland, OR		
	Harborview Medical Center, Seattle, WA		
	Sacred Heard Medical Center, Spokane, WA		
South Central	University of Alabama, Birmingham, AL	16.5	15.0
	University Hospital, Oklahoma City, OK		
	Methodist Hospital, Memphis, TN		
	Vanderbilt University, Nashville, TN		
	Children's Medical Center, Dallas, TX		
	Providence Memorial Hospital, El Paso, TX		
	Texas Children's Hospital, Houston, TX		
Southeast	Shands Hospital at Univ. of Florida, Gainesville, FL	14.6	19.2
	Mount Sinai Medical Center, Miami Beach, FL		
	Medical College of Georgia, Augusta, GA		
	Pikeville United Methodist, Pikeville, KY		
	University of Louisville Hospital, Louisville, KY		
	Carolinas Medical Center, Charlotte, NC		
	Fairfax Hospital, Falls Church, VA		
	University of Virginia Medical Center, Charlottesville, VA		
	W. Virginia University Hospital, Morgantown, WV		
Southwest	Maricopa Medical Center, Phoenix, AZ	14.7	14.3
	Good Smaritan Regional Medical Center, Phoenix, AZ		
	Tucson Medical Center, Tucson, AZ		
	Loma Linda University Medical Center, Loma Linda, CA		
	St. Joseph Hospital, Orange, CA		
	University Hospital, Denver, CO		

RESULTS

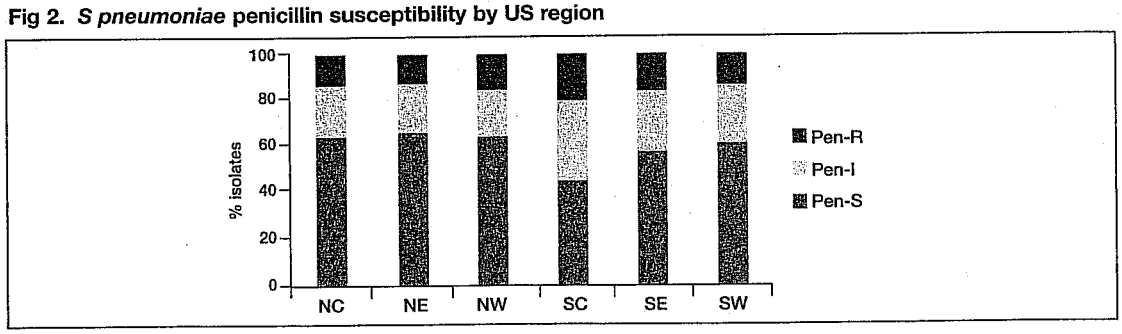
- A total of 60.1% of *S pneumoniae* were susceptible to penicillin, 24.8% were intermediate, and 15.1% were resistant (Fig 1)

Fig 1. *S pneumoniae* penicillin susceptibility



- Highest rates of penicillin resistance were in the South Central and Southeast regions (Fig 2)

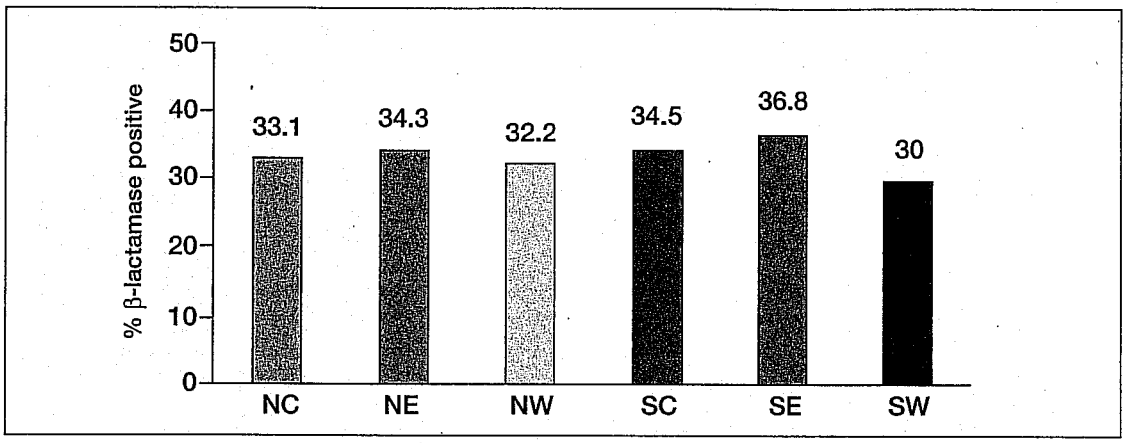
Fig 2. *S pneumoniae* penicillin susceptibility by US region



RESULTS (cont'd)

- Highest rates of β-lactamase production were in the South Central and Southeast regions (Fig 3)

Fig 3. Percent β-lactamase–positive *H influenzae* by US region



MIC Results for *S pneumoniae* (Table 3)

Table 3. *S pneumoniae* Summary of Susceptibility Data (N = 3,241)

			% Isolates			Interpretive Criteria (µg/ml)		
Antimicrobical Agent	**MIC_{50}**	**MIC_{90}**	**Susceptible**	**Intermediate**	**Resistant**	**Susceptible**	**Intermediate**	**Resistant**
Amoxicillin/clavulanate[a]	0.03	2	96.3	2.9	0.8	≤2	4	≥8
Penicillin	0.03	2	60.1	24.8	15.1	≤0.06	0.12–1	≥2
Cefixime	0.5	32	61.7	–	–	–	–	–
Cefprozil	0.25	8	70.0	–	–	–	–	–
Ciprofloxacin	2	4		0.9% at >8 µg/ml		–	–	–
Clarithromycin[a]	0.125	16	73.2	0.5	26.3	≤0.25	0.5	≥1
			(73.7)	(0.8)	(25.5)	(≤0.5)	(1)	(≥2)

[a]Breakpoints approved at 7 June 1998 NCCLS meeting based on microbiology, animal, pharmacokinetic, pharmacodynamic, and clinical data, to be officially published January 2000. [b]MIC results are approximately one 2-fold dilution higher than reference MIC results due to incubation in CO_2. The breakpoint adjusted for this CO_2 effect and associated susceptibility rates are in parentheses.

- Of the 3,241 *S pneumoniae* isolates, 96.3% were susceptible to amoxicillin/clavulanic acid, compared with a 60.1% susceptible rate for penicillin
  - All the penicillin-susceptible strains, 99.6% of the penicillin-intermediate strains, and 76.0% of the penicillin-resistant strains were susceptible to amoxicillin/clavulanic acid
- 73% of *S pneumoniae* were susceptible to clarithromycin
  - 93.0% of penicillin-susceptible strains, 53.3% of penicillin-intermediate strains, and 26.6% of penicillin-resistant strains were susceptible to clarithromycin
- Interpretive criteria (susceptible, intermediate, and resistant categories) have not been defined for cefixime, cefprozil, and ciprofloxacin against *S pneumoniae*
  - MIC_{90}s for these drugs were higher than for penicillin
  - Nonetheless, these drugs should be evaluated individually based on their peak serum levels and time above MIC
  - 0.9% of *S pneumoniae* isolates tested had elevated ciprofloxacin MICs (>8 µg/ml)

MIC Results for *H influenzae* (Table 4)

Table 4. *H influenzae* Summary of Susceptibility Data (N = 3,334)

			% Isolates			Interpretive Criteria		
Antimicrobical Agent	**MIC_{50}**	**MIC_{90}**	**Susceptible**	**Intermediate**	**Resistant**	**Susceptible**	**Intermediate**	**Resistant**
Amoxicillin/clavulanate	1	2	100	–	0	≤4/2	–	≥8/4
Ampicillin	0.5	>256	64.8	3.5	31.7	≤1	2	≥4
Cefixime	0.06	0.06	100	–	0	≤1	–	–
Cefprozil	4	32	82.6	7.5	9.9	≤8	16	≥32
Ciprofloxacin	0.03	0.03	100	–	0	≤1	–	–
Clarithromycin[a]	16	32	46.1	37.7	16.2	≤8	16	≥32
			(83.8)	(13.4)	(2.8)	(≤16)	(32)	(≥64)

[a]MIC results are approximately one 2-fold dilution higher than reference MIC results due to incubation in CO_2. The breakpoints adjusted for this CO_2 effect and associated susceptibility rates are in parentheses.

- All *H influenzae* strains were susceptible to amoxicillin/clavulanic acid, cefixime, and ciprofloxacin
- The cefprozil rate was significantly lower at 82.5%
- The rate of β-lactamase–negative ampicillin-resistant (BLNAR) strains remains very low (0.03%)
- *H influenzae* clarithromycin values were affected by the CO_2 incubation used in the E-test procedure
  - Results are typically one 2-fold dilution higher than reference MIC results. Thus, clarithromycin *H influenzae* susceptibility rates are lower than in other published studies[2]
  - However, clinical studies that have used bacteriologic eradication as a measure of outcome indicate that lower breakpoints for *H influenzae* versus macrolides for otitis media may be more appropriate[4-6]

RESULTS (cont'd)

- The highest rates of β-lactamase production were in patients younger than 2 years (41.8%) and in those from 3 to 10 years (37.3%)
  The penicillin-resistant rate (comprising both intermediate and resistant isolates) was nearly 50% in patients younger than 2 years and 45% in those 3 to 10 years
  –Both of these rates are higher than the overall average resistance rate of 40% (Table 5)

Table 5. Age Variation in β-Lactam Susceptibility of *S pneumoniae* and *H influenzae*

	H influenzae		*S pneumoniae*		
Age (yr)	**No. Isolates**	**% β-Lactamase Positive**	**No. Isolates**	**% Pen-I**	**% Pen-R**
≤2	578	41.8	729	30.8	18.8
3–10	375	37.3	342	26.3	18.7
11–20	221	32.3	138	20.3	12.3
21–30	202	29.4	180	31.7	16.7
31–40	309	28.5	292	20.9	13.4
41–50	336	32.9	317	20.2	9.1
51–60	365	30.7	307	26.4	14.0
61–70	359	31.0	324	23.8	13.9
>70	473	34.0	462	19.0	13.4
Unknown	116	26.7	150	22.0	16.7
TOTAL	3334	33.8	3241	24.8	15.1

Table 6. Summary of MIC Results by US Region

		Ampicillin* Penicillin†	Amoxicillin/ Clavulanic Acid	Cefixime	Cefprozil	Ciprofloxacin	Clarithromycin‡
				Haemophilus influenzae			
TOTAL N=3334	MIC_{90}	>256	2	0.06	16	0.03	32
	% S	64.8	100	100	82.6	100	46.1 (83.8)
N CENTRAL n=563	MIC_{90}	64	2	0.06	32	0.03	32
	% S	64.6	100	100	81.4	100	37.3 (81.2)
N EAST n=818	MIC_{90}	>256	2	0.06	16	0.03	32
	% S	64.1	100	100	83.6	100	42.6 (81.0)
N WEST n=335	MIC_{90}	128	2	0.06	16	0.03	32
	% S	65.4	100	100	82.4	100	44.2 (83.9)
S CENTRAL n=502	MIC_{90}	>256	2	0.06	32	0.03	32
	% S	63.7	100	100	81.5	100	52.7 (85.2)
S EAST n=639	MIC_{90}	>256	2	0.06	32	0.03	32
	% S	63.2	100	100	82	100	53.2 (89.7)
S WEST n=477	MIC_{90}	128	1	0.06	16	0.03	32
	% S	69.2	100	100	85	100	47.2 (82.4)
				Streptococcus pneumoniae			
TOTAL N=3241	MIC_{90}	2	2	32	8	4	16
	% S	60.1	96.3	–	–	–	73.2 (73.7)
N CENTRAL n=605	MIC_{90}	2	1	32	8	4	16
	% S	64.3	97	–	–	–	76.2 (76.6)
N EAST n=898	MIC_{90}	2	1	16	8	4	4
	% S	66.2	96.8	–	–	–	77.1 (77.4)
N WEST n=254	MIC_{90}	2	1	32	16	4	4
	% S	64.6	96.9	–	–	–	80.3 (81.5)
S CENTRAL n=519	MIC_{90}	2	2	32	16	4	32
	% S	44.7	94.9	–	–	–	59.4 (60.0)
S EAST n=472	MIC_{90}	2	2	32	8	4	16
	% S	57	94.5	–	–	–	71.3 (72.2)
S WEST n=493	MIC_{90}	2	2	32	8	4	32
	% S	61	97.3	–	–	–	74.9 (75.3)

*H influenzae
†S pneumoniae
‡Clarithromycin MIC results are approximately one 2-fold dilution higher than reference MIC results due to incubation in CO_2. Susceptibility rates based on a breakpoint that is one 2-fold dilution higher are in parentheses.

CONCLUSIONS

- β-Lactam resistance remains high in both species and macrolide resistance is increasing in *S pneumoniae* compared to prior studies[2,7]
- Although quinolone resistance in *S pneumoniae* is rare, its emergence is a serious consideration for the clinician
- Amoxicillin/clavulanic acid was the most active oral agent against *S pneumoniae*
- BLNAR *H influenzae* strains remain rare
- Amoxicillin/clavulanic acid, cefixime, and ciprofloxacin were the most active agents against *H influenzae*
- β-Lactam resistance is highest in the South Central and Southeast regions of the United States and in children younger than 10 years

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