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Resistance surveillance of *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* isolated in the United States, 1997–1998

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A national antimicrobial resistance surveillance study was conducted from December 1997 to May 1998 to determine the prevalence of antimicrobial resistance in 6620 clinical isolates of *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis*. In this centralized study, which involved 163 institutions located in 43 states, we determined MICs for representatives of five antimicrobial classes: β-lactams (penicillin, co-amoxiclav, cefuroxime, ceftriaxone), macrolides (azithromycin, clarithromycin), co-trimoxazole, glycopeptides (vancomycin) and fluoroquinolones (levofloxacin). In most *S. pneumoniae* isolates, all antimicrobials were to be found active, but amongst penicillin-resistant isolates (MICs ≥ 2 mg/L), resistance to other β-lactams, macrolides and co-trimoxazole was common. For vancomycin and levofloxacin, however, activity was not associated with penicillin resistance. The prevalence of penicillin-nonsusceptible (intermediate and resistant) pneumococci was highest in the South Atlantic (44%) and East South Central (43%) regions and lowest in the Mid-Atlantic (28%) and New England (28%) regions. Resistance to β-lactams, macrolides and co-trimoxazole was more commonly found amongst respiratory isolates than blood isolates and in strains from patients ≤ 12 years old than from older patients. β-lactamase, which was detected in 33% of *H. influenzae* and 92% of *M. catarrhalis* strains, did not affect the activity of the β-lactams under study other than ampicillin. Certain agents, such as vancomycin and the fluoroquinolones, remain highly active, and well-designed surveillance systems that monitor MIC distributions would be needed to detect a potential for reduced susceptibility. In addition, surveillance programmes should be designed to collect information about associated resistance as well as differences in prevalence associated with region, specimen source and patient age.

Introduction

Each year, 7 million cases of otitis media, 500,000 cases of pneumonia, 50,000 cases of bacteraemia and 3000 cases of meningitis are attributed to *Streptococcus pneumoniae* in the USA alone.[1] The importance of this pathogen, coupled with the rise in antimicrobial resistance amongst pneumococci,[2–5] makes evident the need for comprehensive surveillance of resistance. Also of concern is that resistance to penicillin frequently signals resistance to other antimicrobial agents, including other penicillins, cephalosporins, macrolides, lincosamides, tetracycline and co-trimoxazole.[2,5–10] Other bacteria frequently implicated in respiratory infections are *Haemophilus influenzae* and *Moraxella catarrhalis*.[11] For these organisms, resistance to β-lactams is of particular concern.

To monitor antimicrobial resistance patterns, comprehensive surveillance studies that provide a variety of information are needed.[12] Such information should include changes in resistance to certain antimicrobials, age-associated resistance, regional variations in resistance and specimen source differences. Changes in resistance should be monitored with quantitative data as well as categorical susceptibility results, in order to detect subtle but potentially significant trends. Such comprehensive analyses rarely appear in the literature. This report, which documents the

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findings of such a surveillance study, was conducted in the USA with isolates collected between December 1997 and May 1998. To our knowledge, no results have been reported with strains isolated this recently.[5,9,10,13,14]

Materials and methods

Bacterial strains

For this surveillance study, a total of 6620 isolates of 1997–1998 respiratory pathogens were examined: 4148 isolates of *S. pneumoniae*, 1760 isolates of *H. influenzae* and 712 isolates of *M. catarrhalis*. We collected isolates from 163 USA institutions, which were located in 43 states and ranged in size from <100 to >1000 beds. The isolates were collected without regard to specimen source, and a laboratory coding system was used to prevent the acquisition of duplicate strains from the same patient. We performed confirmatory tests to verify the site's identification of the isolate and subcultured isolates on sheep blood agar plates (*S. pneumoniae* and *M. catarrhalis)* or chocolate agar (*H. influenzae*).[15]

Antibiotics and susceptibility testing

To evaluate the antimicrobial activity of nine agents against respiratory isolates, representatives from five antimicrobial classes were tested: β-lactams (penicillin, co-amoxiclav, cefuroxime, ceftriaxone), macrolides (azithromycin, clarithromycin), co-trimoxazole, glycopeptides (vancomycin) and fluoroquinolones (levofloxacin).

Broth microdilution plates (Accumed, Chicago, IL, USA) were used to determine MICs according to the recommended procedures of the National Committee for Clinical Laboratory Standards (NCCLS).[16] Overnight growth was suspended in diluent to produce a turbidity equivalent to a 0.5 McFarland standard (approximately 1×10^8 cfu/mL), and this suspension was used to inoculate broth microdilution plates to obtain a final inoculum of 5×10^5 cfu/mL. The media used were cation-adjusted Mueller–Hinton broth supplemented with 2–5% lysed horse blood for *S. pneumoniae*, Haemophilus test medium for *H. influenzae* and cation-adjusted Mueller–Hinton broth for *M. catarrhalis*. The MIC plates were incubated at 35°C for 20–24 h in ambient air before reading. Throughout the testing period, *S. pneumoniae* ATCC 49619 and *H. influenzae* ATCC 49247 were used as controls. β-Lactamase production in *M. catarrhalis* and *H. influenzae* isolates was assessed with DrySlide Nitrocefin (Difco Laboratories, Detroit, MI, USA). NCCLS breakpoints were followed to determine susceptible, intermediate and resistant categories of *S. pneumoniae* and *H. influenzae* (Table I). 'Nonsusceptible' was defined as the combination of intermediate and resistant categories. Because NCCLS

Table I. NCCLS interpretative categories for *S. pneumoniae* and *H. influenzae*[16]

	NCCLS interpretative categories (mg/L)		
Antimicrobial agent	susceptible	intermediate	resistant
S. pneumoniae			
penicillin	≤0.06	0.12–1.0	≥2.0
co-amoxiclav	≤0.5/0.25	1.0/0.5	≥2.0/1.0
cefuroxime	≤0.5	1.0	≥2.0
ceftriaxone	≤0.5	1.0	≥2.0
azithromycin	≤0.5	1.0	≥2.0
clarithromycin	≤0.25	0.5	≥1.0
co-trimoxazole	≤0.5/9.5	1.0/19–2.0/38	≥4.0/76
vancomycin[a]	≤1	–	–
levofloxacin	≤2	4	≥8
H. influenzae			
ampicillin	≤1.0	2.0	≥4.0
co-amoxiclav	≤4.0/2.0	–	≥8.0/4.0
cefuroxime	≤4.0	8.0	≥16
ceftriaxone	≤2.0	–	–
azithromycin	≤4.0	–	–
clarithromycin	≤8.0	16	≥32
co-trimoxazole	≤0.5/9.5	1.0/19–2.0/38	≥4.0/76
levofloxacin	≤2	–	–

[a]NCCLS does not recognize strains intermediate or resistant to vancomycin.

has not established susceptibility breakpoints for *M. catarrhalis*, only MIC data were evaluated for these isolates.

Results

The susceptibility profiles of 4148 *S. pneumoniae* isolates are presented according to penicillin susceptibility to show the correlation between penicillin resistance and resistance to other antimicrobials (Table II). The majority (65%) of *S. pneumoniae* isolates were susceptible to penicillin (MICs $\leq$ 0.06 mg/L). The susceptibilities of isolates to β-lactams, macrolides and co-trimoxazole (range 68.1–87.8%) were lower than the susceptibilities to vancomycin (100%) and levofloxacin (99.8%). Of the eight levofloxacin-nonsusceptible strains, one was intermediate (MIC 4 mg/L) and seven were resistant (MIC $\geq$ 8 mg/L) to levofloxacin. Of the four levofloxacin-nonsusceptible isolates that were also intermediate to penicillin, two were resistant to both clarithromycin and co-trimoxazole.

Of the penicillin-susceptible *S. pneumoniae* strains, almost all were susceptible to the other drugs tested. The exceptions were strains not susceptible to macrolides (6.2%) or co-trimoxazole (10.6%). In contrast, for penicillin-resistant *S. pneumoniae* isolates (MICs $\geq$ 2 mg/L), resistance to other β-lactams, macrolides and co-trimoxazole was more common. Amongst penicillin-resistant strains, the proportion of strains resistant to β-lactams ranged from 23.2% for ceftriaxone to 98.7% for cefuroxime, and for other agents, the proportion resistant ranged from 49% for co-trimoxazole to 68.5% for clarithromycin. The susceptibility profiles for penicillin-intermediate *S. pneumoniae* showed much more resistance than the penicillin-susceptible strains and less resistance than the penicillin-resistant isolates. For the fluoroquinolone levofloxacin, the percentage of susceptible strains remained >99%, regardless of penicillin susceptibility status.

To evaluate further the association between resistance to penicillin and resistance to other agents, we analysed resistance to cefuroxime, ceftriaxone, azithromycin, co-trimoxazole and levofloxacin according to penicillin MICs (Figure 1). For azithromycin and co-trimoxazole, resistance occurred even at the lower penicillin MICs and increased as the penicillin MICs increased. Clarithromycin resistance followed a similar pattern (data not shown). No penicillin-susceptible strains were resistant to cefuroxime, but the percentage of strains resistant to cefuroxime began to rise with penicillin MICs in the intermediate category (0.12–1.0 mg/L). Although 11 penicillin-intermediate strains were resistant to ceftriaxone, a concomitant rise in ceftriaxone resistance and penicillin MICs was observed only in strains having high-level penicillin resistance (MIC > 2 mg/L). The eight levofloxacin-nonsusceptible strains were not clustered at any specific penicillin MIC.

The MIC distributions provided in Table III allow more precise examination of the relative antimicrobial activities of the various antimicrobial agents against *S. pneumoniae*. Clusters of strains within one or two doubling dilutions of the susceptibility breakpoint signal a risk of future susceptibility category shifts. For example, vancomycin-nonsusceptible pneumococci have not been isolated, but our study showed that 25% of isolates had a vancomycin MIC of 0.5 mg/L, which is one doubling dilution lower than

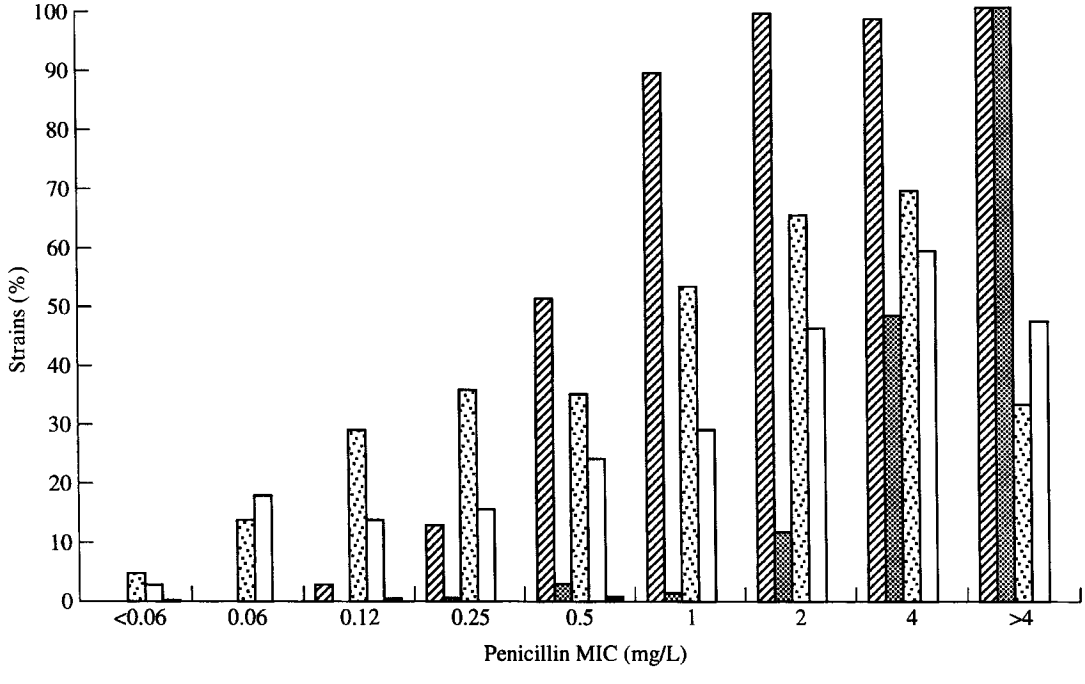

Figure 1. Resistance of *S. pneumoniae* to selected antimicrobials correlated with penicillin MICs. ▨, Azithromycin; □, co-trimoxazole; ▩; ceftriaxone; ■, levofloxacin; □, cefuroxime.

Table II. Activity of nine antimicrobial agents against 1997–1998 clinical isolates of *S. pneumoniae*, according to penicillin-susceptibility phenotype

Antimicrobial agent and phenotype (No. of isolates)	% Susceptible[a]	% Intermediate	% Resistant
Penicillin			
all (4148)	65.1	22.1	12.8
Pen S (2699)	100.0	0.0	0.0
Pen I (915)	0.0	100.0	0.0
Pen R (534)	0.0	0.0	100.0
Co-amoxiclav			
all (4148)	83.3	6.8	9.9
Pen S (2699)	100.0	0.0	0.0
Pen I (915)	78.3	15.8	5.9
Pen R (534)	7.3	25.5	67.2
Cefuroxime			
all (4148)	73.5	3.6	22.9
Pen S (2699)	100.0	0.0	0.0
Pen I (915)	37.4	16.3	46.3
Pen R (534)	0.9	0.4	98.7
Ceftriaxone			
all (4148)	87.8	9.0	3.3
Pen S (2699)	100.0	0.0	0.0
Pen I (915)	90.5	8.3	1.2
Pen R (534)	21.4	55.4	23.2
Azithromycin			
all (4148)	77.1	1.7	21.1
Pen S (2699)	93.8	0.4	5.7
Pen I (915)	54.9	4.6	40.5
Pen R (534)	30.9	3.0	66.1
Clarithromycin			
all (4148)	77.1	0.8	22.0
Pen S (2699)	93.8	0.3	5.9
Pen I (915)	54.9	2.5	42.6
Pen R (534)	30.9	0.6	68.5
Co-trimoxazole			
all (4148)	68.1	17.6	14.3
Pen S (2699)	89.4	5.7	4.9
Pen I (915)	41.3	36.7	22.0
Pen R (534)	6.2	44.8	49.0
Vancomycin			
all (4148)	100.0	0.0	0.0
Pen S (2699)	100.0	0.0	0.0
Pen I (915)	100.0	0.0	0.0
Pen R (534)	100.0	0.0	0.0
Levofloxacin			
all (4148)	99.8	0.0	0.2
Pen S (2699)	99.9	0.0	0.1
Pen I (915)	99.6	0.1	0.3
Pen R (534)	100.0	0.0	0.0

[a]Interpretative breakpoints recommended by the NCCLS (16) for susceptible (S), intermediate (I) or resistant (R).

Table III. MIC distributions of nine antimicrobial agents for 1997–1998 clinical isolates of *S. pneumoniae*[a]

Antimicrobial	Percentage (cumulative percentage) of strains at the following MIC (mg/L)								
	≤0.03	0.06	0.12	0.25	0.5	1	2	4	≥8
Penicillin	57.0 (57.0)	8.1 (65.1)	4.6 (69.7)	4.8 (74.5)	4.6 (79.1)	8.0 (87.1)	9.4 (96.5)	3.1 (99.6)	0.4 (100)
Co-amoxiclav	63.9 (63.9)	4.9 (68.8)	4.6 (73.4)	4.3 (77.7)	5.6 (83.3)	6.8 (90.1)	5.9 (96.0)	2.6 (98.6)	1.4 (100)
Cefuroxime			58.5 (58.5)[b]	10.4 (68.9)	4.5 (73.4)	3.6 (77.0)	8.0 (85.0)	9.8 (94.8)	5.2 (100)
Ceftriaxone	57.9 (57.9)	7.3 (65.2)	6.8 (72.0)	6.9 (78.9)	9.0 (87.9)	9.0 (96.9)	1.9 (98.8)	1.2 (99.9)	0.1 (100)
Azithromycin	36.0 (36.0)	34.7 (70.7)	5.3 (76.0)	0.7 (76.7)	0.5 (77.2)	1.7 (78.9)	4.6 (83.5)	6.9 (90.4)	9.6 (100)
Clarithromycin	74.0 (74.0)	1.8 (75.8)	0.5 (76.3)	0.8 (77.1)	0.8 (77.9)	3.1 (81.0)	6.0 (87.0)	4.7 (91.7)	8.3 (100)
Co-trimoxazole	7.8 (7.8)	21 (28.8)	29.2 (58)	6.2 (64.2)	3.9 (68.1)	4.0 (72.1)	13.6 (85.7)	10.3 (96)	4.0 (100)
Vancomycin		1.4 (1.4)[c]	7.1 (8.5)	65.8 (74.3)	25.3 (99.6)	0.4 (100)			
Levofloxacin	1.6 (1.6)	0.1 (1.7)	0.8 (2.5)	11 (13.5)	70.7 (84.2)	14.9 (99.1)	0.7 (99.8)	0 (99.8)	0.2 (100)

[a]Shading denotes intermediate MICs, according to recommendations of the NCCLS for all drugs under study other than vancomycin, for which the susceptible breakpoints are shaded instead.
[b]The values are for ≤0.12 mg/L.
[c]The values are for ≤0.06 mg/L.

the NCCLS breakpoint (MIC ≤ 1 mg/L) and 66% of strains had a vancomycin MIC of 0.25 mg/L, which is two doubling dilutions lower than the breakpoint.

The USA was divided into the nine regions established by the United States Bureau of the Census, as shown in Figure 2, which depicts the geographical distribution of antimicrobial resistance amongst *S. pneumoniae* and shows the extent to which resistance patterns varied. Penicillin resistance was highest in the South Atlantic (44%) and East South Central (43%) regions and lowest in the New England (28%) and Mid-Atlantic regions (28%). The geographical distribution of ceftriaxone resistance was similar to that of penicillin with the highest prevalence of resistance occurring in the South Atlantic (17%) and East South Central (18%) regions, twice as high as the prevalence observed in the East North Central region (9%). Similarly, the prevalence of azithromycin resistance in the East South Central region (32%) was twice that in New England (16%). The resistance prevalence for co-trimoxazole was second only to penicillin in all regions, except New England, where the prevalence of penicillin resistance (28%) was lower than that of co-trimoxazole resistance (29%). The highest prevalence of levofloxacin resistance (1%) was in the East South Central region.

In Table IV, the susceptibility profiles of blood isolates of *S. pneumoniae* are compared with the profiles of respiratory isolates. For most of the antimicrobial agents under study, the percentage of susceptible isolates was higher amongst blood isolates than respiratory isolates. Amongst blood isolates, the percentage of strains susceptible to β-lactams ranged from 73.2% for penicillin to 90.7% for ceftriaxone. For co-trimoxazole and the macrolides, the proportion susceptible ranged between 74.0% and 83.1%. Of the eight levofloxacin-nonsusceptible *S. pneumoniae* isolates, one was a blood isolate and seven were from the respiratory tract.

S. pneumoniae susceptibility data analysed according to patient age are shown in Table V. Of the isolates collected for this study, 82% were from patients >12 years of age. For every antimicrobial agent, except vancomycin and levofloxacin, the proportion of nonsusceptible isolates was greater for the ≤12 year age group than for the >12 year age group. For example, 67% of isolates from the >12 year age group were susceptible to penicillin while only 54% of isolates from the ≤12 year age group were penicillin susceptible.

Surveillance of *H. influenzae* isolates revealed that 33% produced β-lactamase and all β-lactamase-negative isolates were ampicillin susceptible (data not shown). With the exception of ampicillin, the production of β-lactamase had little effect on the activity of other β-lactams under study; all isolates of *H. influenzae* were susceptible to the cephalosporins tested. MIC distributions obtained with the *H. influenzae* isolates are shown in Table VI. Resistance to co-trimoxazole (MIC ≥ 4/76 mg/L) occurred in 22% of strains, but resistance to co-amoxiclav (MIC ≥ 8/4 mg/L)

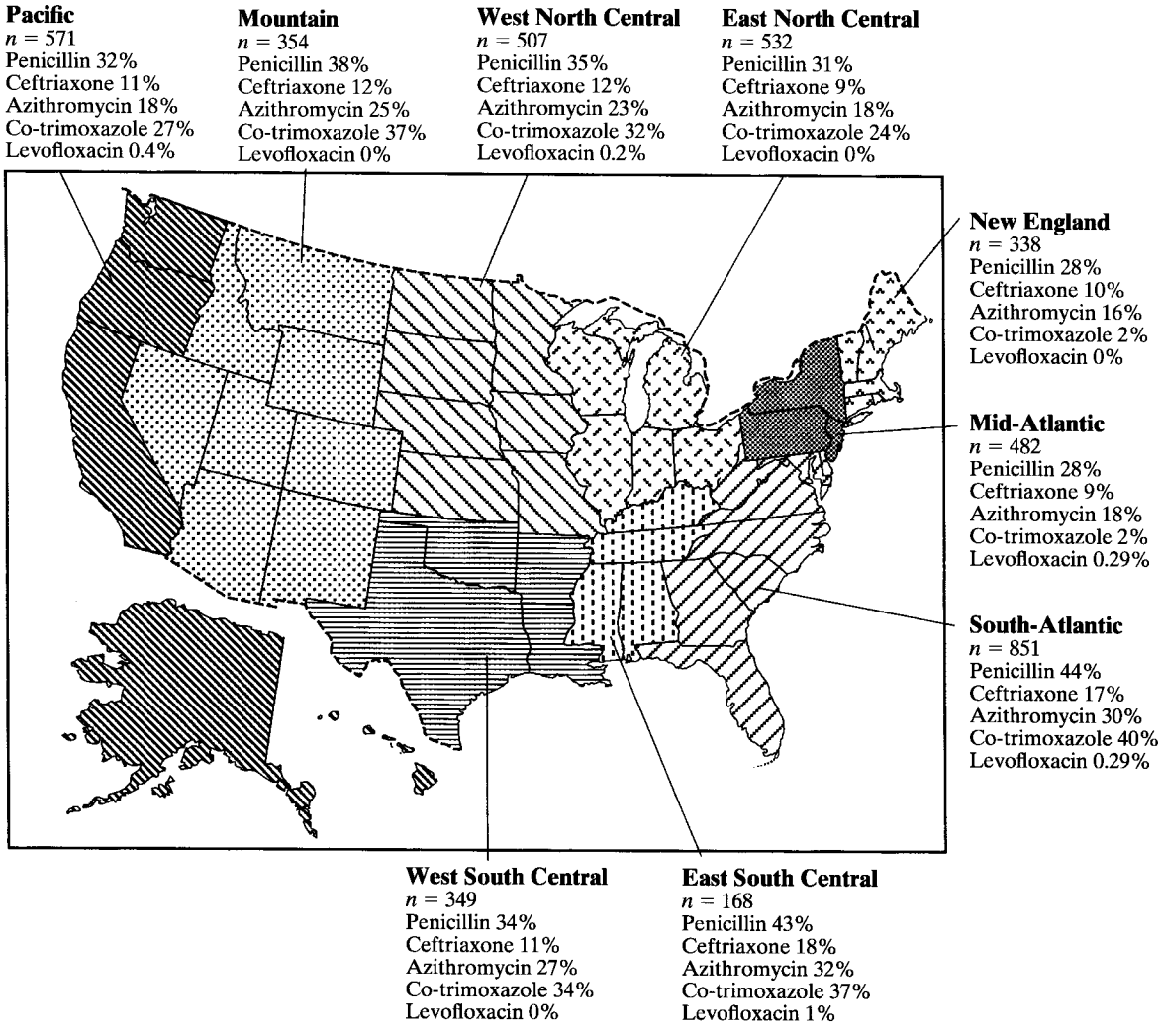

Figure 2. Geographical distribution of the prevalence of antimicrobial nonsusceptibility among *S. pneumoniae* in the USA. States were assigned to the regions established by the US Bureau of the Census.

was rare (0.2%). For the two macrolides, the distribution of MICs indicates the greater activity of azithromycin (MICs $\leq$ 1 mg/L were observed for 83.5% of isolates for azithromycin but only 5.5% for clarithromycin), but the prevalence of susceptible strains was similar for azithromycin (97.3%, MIC $\leq$ 4 mg/L) and clarithromycin (94.2%, MIC $\leq$ 8 mg/L). An MIC of >4 mg/L of azithromycin was observed in one isolate and MICs of >32 mg/L of clarithromycin were detected in four isolates.

MIC distributions obtained with *M. catarrhalis* isolates are shown in Table VII. Of the *M. catarrhalis* tested 92% produced β-lactamase (data not shown), and 84% had ampicillin MICs $\geq$ 0.5 mg/L. Of the β-lactamase positive isolates, 58 (9%) were susceptible to ampicillin (MICs $\leq$ 0.25 mg/L) (data not shown). A clarithromycin MIC of 4 mg/L was found for one isolate and co-trimoxazole MICs of 4 mg/L were observed for three strains.

Discussion

Although reduced susceptibility in pneumococci was described more than 30 years ago, today those resistant strains would be classified as intermediate (MIC 0.1–1.0 mg/L). With the exception of the South African outbreak in the late 1970s,[17] penicillin resistance increased slowly over the first two decades and caused few clinical problems. Through the 1980s, the prevalence of nonsusceptibility in the USA was generally <5% and most of the strains with decreased susceptibility were intermediate in resistance.[3,4] In the early 1990s, however, the prevalence of nonsusceptibility increased sharply to approximately 17% but <3% of strains had high-level resistance.[18] Since this early 1990s study, penicillin resistance has continued to rise so that approximately one-third of isolates in the USA now have decreased susceptibility.[5] One of the more significant changes, however, has been the increase in the prevalence

Table IV. Resistance in *S. pneumoniae* isolates from blood and respiratory specimens

	Blood isolates (n = 1177)			Respiratory isolates (n = 2647)		
Antimicrobial	% susceptible[a]	% intermediate	% resistant	% susceptible	%intermediate	% resistant
Penicillin	73.2	17.5	9.3	61.3	24.3	14.4
Co-amoxiclav	88.4	4.1	7.5	80.9	8.1	10.9
Cefuroxime	81.1	3.1	15.8	70.0	3.9	26.1
Ceftriaxone	90.7	7.7	1.6	86.7	9.5	3.8
Azithromycin	83.1	0.4	16.5	74.4	2.3	23.3
Clarithromycin	83.1	0.3	16.7	74.4	1.1	24.6
Co-trimoxazole	74.0	13.3	12.7	65.5	19.7	14.8
Vancomycin	100.0	0.0	0.0	100.0	0.0	0.0
Levofloxacin	99.9	0.0	0.1	99.7	0.0	0.2

[a]Susceptible, intermediate and resistant interpretative categories as recommended by the NCCLS.[13]

Table V. Antimicrobial susceptibility of *S. pneumoniae* to nine antimicrobial agents, by age group

	⩽12 years (n = 738)			>12 years (n = 3410)		
Antimicrobial	% susceptible[a]	% intermediate	% resistant	% susceptible	% intermediate	% resistant
Penicillin	54.1	26.0	19.9	67.4	21.2	11.4
Co-amoxiclav	75.9	8.9	15.2	84.9	6.3	8.8
Cefuroxime	61.5	4.6	33.9	76.0	3.4	20.6
Ceftriaxone	81.2	12.9	6.0	89.2	8.1	2.7
Azithromycin	68.2	2.3	29.5	79.1	1.6	19.3
Clarithromycin	68.2	1.4	30.5	79.1	0.7	20.2
Co-trimoxazole	55.6	22.8	21.7	70.8	16.5	12.7
Vancomycin	100.0	0.0	0.0	100.0	0.0	0.0
Levofloxacin	100.0	0.0	0.0	99.8	0.0	0.2

[a]Susceptible, intermediate and resistant interpretative categories as recommended by the NCCLS.[13]

of strains with high-level resistance to about 14% in 1996–1997[5] and 16% in 1997.[9] The increase in penicillin resistance in *S. pneumoniae* takes on added importance, since strains developing penicillin resistance frequently exhibit resistance to other classes of drugs normally used to treat respiratory tract infections, e.g. other β-lactams, macrolides, tetracyclines and sulphonamides (including co-trimoxazole).[2,5–10] Because most respiratory tract infections are treated empirically, surveillance that tracks penicillin resistance and associated resistance to other antimicrobials is an important component in eventually understanding the potential impact of this resistance on public health.

In a surveillance study that involved strains isolated in 1994–1995, Doern *et al.*[2] reported that 9.5% of 1527 *S. pneumoniae* isolates were resistant to penicillin (MIC $\geqslant$ 2 mg/L). Subsequently, several studies conducted with pneumococci isolated in 1996 and 1997 showed high-level penicillin resistance (MIC > 1 mg/L) that ranged from 11% to 16%.[5,8,9,19] This 1997–1998 study, which indicated that 13% of isolates were resistant, corroborates the findings of the 1996–1997 studies and suggests that penicillin resistance has increased since the 1994–1995 study by Doern *et al.*[2] In addition, the prevalence of penicillin-intermediate strains increased from 14% in 1994–1995,[2] to 20% in 1996–1997[5] and to 22% in 1997–1998.

For other β-lactam agents, the prevalence of resistance observed in this study was similar to earlier reports,[2,5] but our results suggest that macrolide resistance in *S. pneumoniae* is rising. For 1992 and 1993 isolates, Felmingham and co-workers found 3.2% azithromycin resistance and 3.5% clarithromycin resistance;[20] Doern and colleagues reported 10% resistance to both agents amongst 1994–1995 isolates,[2] Thornsberry *et al.*[5] reported 18% resistance to clarithromycin amongst 1996–1997 isolates, and in 1997–1998, we found 21% resistance to azithromycin and 22% resistance

Table VI. MIC distributions of eight antimicrobial agents for 1997–1998 clinical isolates of *H. influenzae*[a]

Antimicrobial	Percentage (cumulative percentage) of strains at the following MIC (mg/L)										
	≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	≥16
Ampicillin				14.9 (14.9)	35.3 (50.3)	11.4 (61.7)	4.8 (66.5)	0.6 (67.1)	1.3 (68.4)	4.8 (73.2)	26.8 (100)
Co-amoxiclav	0.5 (0.5)	1.0 (1.5)	0.8 (2.3)	3.6 (6.0)	21.9 (27.9)	39.0 (66.9)	23.0 (89.9)	8.0 (97.8)	1.9 (99.8)	0.2 (99.9)	0.1 (100)
Cefuroxime				2.6 (2.6)	14.0 (16.6)	32.6 (49.2)	37.1 (86.3)	9.5 (95.9)	4.1 (100)		
Ceftriaxone	84.6 (84.6)	10.7 (95.3)	2.0 (97.3)	1.3 (98.6)	0.6 (99.3)	0.3 (99.5)	0.5 (100)				
Azithromycin		0.8 (0.8)	1.8 (2.6)	4.8 (7.4)	6.2 (13.6)	21.1 (34.7)	48.8 (83.5)	13.8 (97.3)	2.6 (99.9)	0.1 (100)[b]	
Clarithromycin	0.3 (0.3)	0.5 (0.8)	0.5 (1.3)	0.8 (2.0)	0.4 (2.4)	0.8 (3.2)	2.3 (5.5)	8.4 (13.9)	40.6 (54.5)	39.7 (94.2)	5.7 (100)
Co-trimoxazole	1.9 (1.9)	4.5 (6.4)	16.6 (23.1)	19.1 (42.2)	21.5 (63.8)	14.0 (77.8)	5.7 (83.5)	2.7 (86.2)	3.1 (89.3)	10.7 (100)	
Levofloxacin	90.0 (90.0)	6.9 (96.9)	1.1 (98.0)	0.7 (98.7)	0.3 (99.0)	0.4 (99.4)	0.6 (100)				

[a]Shaded areas represent NCCLS intermediate interpretative breakpoints, except for levofloxacin, ceftriaxone and azithromycin, which only have susceptible breakpoints.[13] Co-amoxiclav is shaded at the resistant breakpoint since there is no intermediate category.
[b]This value represents ≥8 mg/L.

Table VII. MIC distributions of eight antimicrobial agents for 1997–1998 clinical isolates of *M. catarrhalis*

Antimicrobial	Percentage (cumulative percentage) of strains at the following MIC (mg/L)										
	≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	≥16
Ampicillin				10.4 (10.4)	6.0 (16.4)	8.6 (25.0)	15.7 (40.7)	20.5 (61.2)	21.1 (82.3)	13.2 (95.5)	4.5 (100)
Co-amoxiclav	10.1 (10.1)	18.3 (28.4)	10.4 (38.8)	16.6 (55.3)	34.4 (89.7)	9.8 (99.6)	0.3 (99.9)	0 (99.9)	0 (99.9)	0.1 (100)	
Cefuroxime				2.0 (2.0)	10.1 (12.1)	27.9 (40.0)	35.7 (75.7)	21.9 (97.6)	2.4 (100)		
Ceftriaxone	17.4 (17.4)	13.6 (31.0)	5.9 (36.9)	6.2 (43.1)	20.8 (63.9)	26.1 (90.0)	8.8 (98.9)	1.1 (100)			
Azithromycin		82.7 (82.7)	13.2 (95.9)	1.8 (97.8)	0.6 (98.3)	0.6 (98.9)	0.8 (99.7)	0.3 (100)			
Clarithromycin	2.5 (2.5)	11.1 (13.6)	62.8 (76.4)	18.5 (94.9)	3.7 (98.6)	0.7 (99.3)	0.1 (99.4)	0.4 (99.9)	0.1 (100)		
Co-trimoxazole	2.8 (2.8)	8.1 (11.0)	20.9 (31.9)	29.8 (61.7)	27.9 (89.6)	6.6 (96.2)	3.2 (99.4)	0.1 (99.6)	0.4 (100)		
Levofloxacin	6.9 (6.9)	74.6 (81.5)	15.2 (96.6)	1.7 (98.3)	0.4 (98.7)	0.7 (99.4)	0.6 (100)				

to clarithromycin. In addition, the prevalence of co-trimoxazole resistance may be increasing amongst *S. pneumoniae*. For 1993 isolates, Felmingham *et al.* reported that 7.4% were resistant to co-trimoxazole,[20] Doern and co-workers found 18%,[2] and the data presented here indicate a resistance prevalence of 14.3%.

As reported in other studies,[2,5,8] the findings with 1997 and 1998 pneumococcal strains indicate that both vancomycin and levofloxacin continue to maintain a high degree of activity against pneumococci. Our study shows that vancomycin resistance was not detected and levofloxacin resistance remains rare in the USA (0.2%). In a 1997–1998 study of 5640 strains of pneumococci also conducted in the USA, evaluation of ciprofloxacin activity (MIC_{90} 1 mg/L) indicated that fluoroquinolone resistance in general is rare.[21] In a similar study of 1879 pneumococci collected in Asia and Europe, levofloxacin resistance was detected in 0.9% of strains isolated in Japan, 0.8% of strains from China, 0.4% of strains from Germany and none of the strains from France, Italy, Spain or the UK.[22]

Of the institutions participating in this 1997–1998 study, 131 also participated in the 1996–1997 study by Thornsberry *et al.*[5] No institution that isolated a levofloxacin-resistant strain in the 1996–1997 study isolated such a strain during the 1997–1998 study. These longitudinal findings indicate that while fluoroquinolone resistance can be encountered in pneumococci, no evidence yet exists of clonal spread and wider dissemination of this currently sporadic resistance. These findings are also consistent with those reported by Plouffe *et al.*, who monitored isolates from three hospitals for 3 years and did not note clonal dissemination of fluoroquinolone resistance.[23]

Previous studies[2,5–10] established the association between penicillin resistance and resistance to other β-lactams and non-β-lactams alike, thereby making *S. pneumoniae* a multidrug-resistant organism. Of the drugs under study, the exceptions to linked resistance are vancomycin and levofloxacin. Although a recent report from Northern Ireland indicates a potential for a correlation between fluoroquinolone resistance and penicillin resistance,[24] our results (Table II, Figure 1), and those of others that included large numbers of isolates,[2,5,8,10,21,22] have not established any trends that would suggest a potential link between resistance to β-lactams and fluoroquinolones in the USA. As shown in Figure 1, resistance to several agents increased with incremental increases in penicillin MICs, but resistance to certain agents (e.g. co-trimoxazole and azithromycin) began even before penicillin MICs reached the intermediate breakpoint (MIC 0.12 mg/L). In contrast, resistance to other agents such as cefuroxime did not occur or increase significantly until the penicillin MIC reached 0.5 mg/L. This MIC-based analysis indicates that there may be stages in the development of penicillin resistance that result in a strain being more prone to acquisition of resistance to other agents. For co-trimoxazole and macrolides, reduced susceptibility may occur before intermediate or high-level penicillin resistance is achieved, but for cefuroxime and ceftriaxone, resistance is rarely encountered in the absence of penicillin nonsusceptibility.[2,5]

Studying MIC distribution data enables population trends to be followed so that impending changes may be detected before interpretative categories are breached or MIC_{90} values shift. This practice allows for detection of subtle but potentially significant changes in biological levels of resistance before clinically relevant levels of resistance are achieved. For example, the distribution data in Table III show that 8% of the *S. pneumoniae* isolates are one dilution below the penicillin intermediate breakpoint and a second cluster is one dilution below the resistant breakpoint. Examining MIC distributions will enable the detection of subtle changes in susceptibility to vancomycin and levofloxacin, should they occur.

Surveillance not only needs to provide a broad or global view of resistance to heighten our awareness about the risk of an organism becoming resistant but must also provide data on a local or regional level to inform communities about the scope of their local problems. This need is underscored in Figure 2 where regional variations in resistance amongst pneumococci are readily noted. Our results confirm those of Ballow *et al.*[19] and Thornsberry *et al.*,[5] who found that the lowest prevalences of susceptibility for penicillin, cephalosporins and macrolides amongst *S. pneumoniae* were in the Southeast and East South Central regions of the USA. Our study showed that penicillin susceptibility was lowest in the South Atlantic (56%) and highest in the Northeast (72%) and Mid-Atlantic (72%). Overall, little variation was noted in the geographical distribution of penicillin susceptibility between the 1996–1997 study by Thornsberry and co-workers[5] and the 1997–1998 study reported here.

The prevalence of resistance may vary with the site of infection and the age of the patient from whom the strains were isolated. Analysis of the 1997–1998 surveillance data according to site of infection suggested that resistance to all agents was more prevalent amongst respiratory isolates than amongst blood isolates, which confirmed other studies.[2,8] Although the prevalence of resistance amongst blood isolates appears to lag behind that of respiratory isolates, resistance is not uncommon amongst strains involved in these types of infection.

Consistent with other recent studies, our findings indicate that resistant pneumococcal strains are more likely to be isolated from children than from adults.[2,6,7] The differences in resistance patterns between organisms from these two age groups may be attributed to the higher level of antimicrobial use in the paediatric population and the opportunity for transmission of resistant strains in day-care settings. From that perspective, should fluoroquinolone resistance develop to an appreciable extent in pneumococci, it will be of interest to note early on if resistance occurs in a paediatric population that essentially is not exposed to this class of agents. In this study, none of the 738

S. pneumoniae strains isolated from patients ≤12 years old was resistant to levofloxacin. In addition, no levofloxacin-resistant strains were found in this age group in a recent study of antimicrobial resistance in 591 clinical isolates of *S. pneumoniae* from Europe and Asia.[22]

Results of this 1997–1998 study and those of other reports[3,5,13,14,19,25,26] indicate that the antimicrobial susceptibility profiles of *H. influenzae* and *M. catarrhalis* have not changed dramatically in recent years. For *H. influenzae* and *M. catarrhalis* strains isolated in 1997–1998, the levels of β-lactamase production (33% and 92%, respectively) remained similar to the levels reported for 1996–1997 *H. influenzae* isolates (33%[5] and 32%[14]) and *M. catarrhalis* isolates (93%).[5] β-Lactamase-mediated ampicillin resistance amongst *H. influenzae* was reported to be 36% in 1994–1995[25] and 33% in this study. Although none of the β-lactamase-producing *H. influenzae* isolates was susceptible to ampicillin, 9% of β-lactamase-producing *M. catarrhalis* isolates had ampicillin MICs ≤ 0.25 mg/L (which is the NCCLS susceptibility breakpoint for *Staphylococcus aureus*[16]). Doern and co-workers have hypothesized that BRO-2, a β-lactamase associated with low ampicillin MICs, might account for ampicillin susceptibility amongst β-lactamase-positive *M. catarrhalis*.[26] Also, higher-than-expected ampicillin activity might be attributed to inadequate β-lactamase production so that sufficient levels of ampicillin are not inactivated. Although no notable changes have occurred in the activities of antimicrobial agents against either *M. catarrhalis* or *H. influenzae*, the unpredictability of bacterial populations in general dictates that some level of resistance surveillance continue. In addition, because NCCLS breakpoints have not been established for *M. catarrhalis*, MIC distribution data are even more important for resistance surveillance of this species.

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