Worldwide Prevalence of Antimicrobial Resistance in *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* in the SENTRY Antimicrobial Surveillance Program, 1997–1999

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The in vitro activities of numerous antimicrobials against clinical isolates of *Streptococcus pneumoniae, Haemophilus influenzae,* and *Moraxella catarrhalis* from patients with bloodstream and respiratory tract infections in the United States, Canada, Europe, Latin America, and the Asia-Pacific region were studied in the SENTRY Antimicrobial Surveillance Program. Penicillin resistance (minimum inhibitory concentration, ≥ 2 μg/mL) was noted in all 5 geographic regions, and a high and increasing rate of macrolide resistance among *S. pneumoniae* isolates was observed. Elevated rates of resistance to clindamycin, trimethoprim-sulfamethoxazole, chloramphenicol, and tetracycline were seen. β-Lactamase-mediated resistance in *H. influenzae* to amoxicillin and variable trimethoprim-sulfamethoxazole resistance by region were documented. Resistance to several drugs continues to emerge among pneumococci worldwide, but more stable resistance patterns have been noted for *H. influenzae* and *M. catarrhalis*. Continued surveillance of this pathogen group appears to be prudent.

Streptococcus pneumoniae, Haemophilus influenzae, and *Moraxella catarrhalis* are the most common community-acquired respiratory bacterial pathogens, and an increase in their resistance to the orally administered antimicrobial agents used to treat these infections has emerged as a worldwide problem [1]. An important increase in the prevalence of penicillin resistance among *S. pneumoniae* isolates occurred in the early 1990s in the United States [2–5]. Such an increase had previously been observed in other parts of the world [6–11]. More recently, clinical isolates of *S. pneumoniae* with high-level resistance to cefotaxime and ceftriaxone have been reported [2, 12]. Isolates of *S. pneumoniae* that are resistant to the macrolides, tetracycline, chloramphenicol, and trimethoprim-sulfamethoxazole (TMP-SMX), either alone or in combination, are being recovered more and more often in the United States and Canada [8, 13–15]. This problem has also been recognized in Latin America [16, 17], the Asia-Pacific region [18–20], Europe [6, 7, 10, 11, 21], and South Africa [9].

Fluoroquinolone resistance is uncommon among *S. pneumoniae* isolates [22], but there are clear differences in the in vitro activity of different fluoroquinolones against this organism; gatifloxacin, grepafloxacin, moxifloxacin, sparfloxacin, and trovafloxacin are significantly more active than ciprofloxacin and levofloxacin [12, 22].

Resistance of *H. influenzae* to β-lactams by production of β-lactamase has become increasingly more prev-

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alent in the United States and in other parts of the world [11, 23]. In the United States, an increase in the percentage of β-lactamase-producing *H. influenzae* isolates was noted between the periods of 1983–1984 (15%) and 1994–1995 (36%). Since 1996–1997, no significant change in these figures has been noted; contemporary percentages of β-lactamase-producing *H. influenzae* range from 33.4% in 1996–1997 to 31.1% in 1997–1998 [23, 24]. Resistance to ampicillin without β-lactamase production was noted in several countries at rates no higher than 5% [11, 23] but usually <0.5%.

β-Lactamase-producing strains that are resistant to amoxicillin-clavulanate have recently been noted in the United States [23]. In addition, resistance to orally administered cephalosporins, macrolides, and other antimicrobial agents, such as chloramphenicol and tetracycline, has been described, but no increase in their prevalence has been noted. In contrast, the frequency of *H. influenzae* isolates resistant to TMP-SMX showed a marked increase from 1994–1995 (9%) to 1999 (18.2%), at least in the United States [25].

Most clinical isolates of *M. catarrhalis* produce β-lactamase. This has been increasingly noted in the United States [24–27], Europe [11], and other parts of the world since 1976. Since 1992, >90% of clinical isolates of this microorganism have produced β-lactamase [24–27]. Other enzyme-stable β-lactams, macrolides, and tetracyclines are still very active against *M. catarrhalis,* but rates of TMP-SMX resistance as high as 50% have been occasionally reported [25–27].

The principal mechanism of penicillin resistance to β-lactams in *S. pneumoniae* is the production of altered penicillin-binding proteins (PBPs), enzymes that catalyze the terminal stages of murein synthesis, and this resistance leads to at least some degree of cross-resistance to other β-lactam drugs [8]. Two main mechanisms of macrolide resistance in *S. pneumoniae* have been described: a ribosomal methylase (encoded by *erm* genes), referred to as an MLS_B-type resistance mechanism, and a macrolide efflux pump, encoded by *mef* genes (this M phenotype is the predominant form of macrolide resistance in the United States) [8, 28–31]. The development of reduced susceptibility to fluoroquinolones in *S. pneumoniae* has been described [32], and the presence of *parC* and *gyrA* mutations, especially in combination, are found to contribute significantly to high-level resistance. Efflux probably plays a lesser role in reduced susceptibility to some newer fluoroquinolones [33].

In *H. influenzae* and *M. catarrhalis,* the most recognized mechanism of antimicrobial resistance is the β-lactamase production. In *H. influenzae,* TEM-1 is the most common enzyme, whereas ROB-1 is found in a minority of strains [25]. Some ampicillin-resistant *H. influenzae* strains *do not* produce β-lactamases, and in these strains the resistance may be mediated by alterations in PBPs [25]. Some strains of β-lactamase-producing *H. influenzae* are also resistant to amoxicillin-clavulanate [23], and alterations of PBPs associated with TEM-1 or ROB-1 β-lactamases are considered to be the mechanism of resistance [23, 25]. Fluoroquinolone-resistant *H. influenzae* has recently been characterized [34] and is addressed later. Resistance to penicillin, ampicillin, and amoxicillin in *M. catarrhalis* occurs via production of either BRO-1 or BRO-2 β-lactamases [35]. *M. catarrhalis* isolates resistant to several fluoroquinolones, including levofloxacin, have recently been described [36].

Resistance in these microorganisms has been demonstrated in multiple local and international clones, which supports the idea that drug use–mediated selective pressure is the most important factor in the emergence of resistance. However, some increase in resistance also results from clonal dissemination, as has been suggested with regard to *S. pneumoniae* with reduced susceptibility to β-lactams, fluoroquinolones [32], and other antimicrobials [37].

The SENTRY Antimicrobial Surveillance Program was established in 1997 to monitor the predominant pathogens and antimicrobial resistance patterns of nosocomial and community-acquired infections via national and international networks of sentinel hospitals. The goal of this ongoing study is to compare resistance rates in different geographic areas, in systemic as well as respiratory tract isolates, during the years 1997, 1998, and 1999. This study is unique in the large number of isolates included and the many geographic areas represented.

MATERIALS AND METHODS

Study design. The SENTRY Antimicrobial Surveillance Program investigates the longitudinal trends in antimicrobial resistance and the frequency of pathogen occurrence. A total of 5 major objectives address the most common types of infection (objective A, bloodstream infections; objective B, community-acquired respiratory tract infections caused by *S. pneumoniae, H. influenzae,* and *M. catarrhalis;* objective C, pneumonia in hospitalized patients; objective D, skin and soft-tissue or wound infections; and objective E, urinary tract infections) in a prevalence format.

Consecutive isolates (540 strains/year for all objectives per laboratory) were forwarded to the regional monitors for reference-quality antimicrobial susceptibility testing and confirmation of organism identification. Nearly 100,000 bacteria were processed from 1997 through 1999, the majority within the objective A protocols.

Participants and monitors. A total of 3 reference laboratories functioned as monitor sites during the study period. These included the University of Iowa College of Medicine (for the North and Latin American regions, 1997–1999, and for the European region, 1999); Utrecht University in Utrecht, The Netherlands (for Europe, 1997–1998); and the Women's and Children's Hospital in Adelaide, Australia (for the Asia-Pacific

region, 1998–1999). Common reagents and data-processing systems were used.

The number of participating laboratories varied slightly by year and included the following: 5–8 sites in Canada (North American region); 26–28 sites in the United States (North American region); 10 sites in the Latin American region; 12–23 sites in Europe, Israel, and Turkey (the European region); and 17 sites in the Asia-Pacific region (which also includes South Africa). The number of participating laboratories worldwide ranged from 66 in 1997 to 81 in 1998.

Antimicrobial agents. Approximately 70 antimicrobial agents have been tested (25–30 agents/strain) in the SENTRY program since 1997. Representatives from all clinically important antimicrobial classes have been tested, as well as investigational compounds such as linezolid (U100766), evernimicin (SCH27899), quinupristin-dalfopristin, gatifloxacin, and BMS284756 (a novel desfluoroquinolone). Antimicrobials were obtained from their US manufacturers or representatives and were dispensed into dry-form broth microdilution trays (from MicroScan in 1998–1999; from TREK/Sensititre in 1997). Each lot of trays was shared among all monitor sites, and quality control or validation results were satisfactory in all cases.

Isolate identification. The species identity of all isolates was confirmed in coordinating study centers on the basis of Gram stains and colony morphology, pattern of growth on sheep blood and enriched chocolate agars, indole phenyloxidase and catalase reactivity, and results of the sodium deoxycholate solubility test *(S. pneumoniae),* the β-ALA porphyrin test *(H. influenzae)*, and butyrate hydrolysis *(M. catarrhalis).*

Determination of MICs. MICs were determined using a broth microdilution method as described by the National Committee for Clinical Laboratory Standards (NCCLS) [38]. Trays were incubated in ambient air at 35°C–37°C for 20–24 h before visual determination of MICs. A final inoculum concentration of $\sim 5 \times 10^5$ cfu/mL was used and confirmed by colony counts. The following broth media were used: *Haemophilus* test medium for *H. influenzae,* cation-adjusted Mueller-Hinton broth plus 3% lysed horse blood for *S. pneumoniae,* and cation-adjusted Mueller-Hinton broth for *M. catarrhalis.* Daily quality-control testing was conducted with *H. influenzae* American Type Culture Collection (ATCC) 49249 and ATCC 49766, as well as *S. pneumoniae* ATCC 49619. The interpretation of results was directed by the NCCLS standards [39].

RESULTS

Susceptibility patterns among* S. pneumoniae *isolates. MIC data for the 24 antimicrobials tested against *S. pneumoniae, H. influenzae,* and *M. catarrhalis* are reported in tables 1–3. The MIC_{50} and MIC_{90} values of penicillin tested against *S. pneumoniae* were very similar in the 5 geographic areas (table 1). However, rates of penicillin resistance among pneumococci (MIC, $\geq$2 μg/mL) ranged from 6.8% in Canada to 17.8% in the Asia-Pacific region. By weight, the activity of amoxicillin with or without clavulanate was similar to that of penicillin, but the percentage of resistance was lower ($\leq$3.2%) in all 5 regions. Among the 6 oral cephalosporins tested, the highest rates of resistance were observed in the Asia-Pacific region (19.5%–35.7%) and in the United States (16.1%–26.2%); cefpodoxime was the most active agent. Parenteral cephems, cefotaxime, and cefepime showed excellent antipneumococcal activity (1.8%–3.9% resistance), and the highest rates of resistance occurred in the United States (3.9% and 3.7% to cefepime and cefotaxime, respectively).

A high rate of macrolide resistance among *S. pneumoniae* strains was detected (10.4%–38.6% resistance to erythromycin), especially in the Asia-Pacific region (>36.7% of total resistance to the 3 macrolides tested). The activity of these macrolides, according to MIC and percentage of resistant strains, indicated essential equivalence, thus requiring the testing of only 1 representative agent (erythromycin). Resistance to clindamycin was observed more often in the Asia-Pacific region (20.0%) and Europe (15.4%); these rates were more than 3-fold higher than rates in the Western Hemisphere. High rates (14.4%–27.3%) of TMP-SMX resistance were observed in all the geographic areas, especially in the Asia-Pacific region (27.3%), Latin America (23.8%), and the United States (19.8%). Rifampin resistance was observed, especially in Latin America (2.5%). Resistance to chloramphenicol and tetracycline was highest in the Asia-Pacific region (15.8% and 41.7%, respectively). All isolates of *S. pneumoniae* (except 0.1% in Latin America) were susceptible to quinupristin-dalfopristin. Vancomycin MICs of >1 μg/mL were detected in only 0.1% of isolates from Europe and 0.3% of isolates in the Asia-Pacific region.

Ciprofloxacin was only marginally active against *S. pneumoniae* (MIC_{90}, 2 μg/mL). The activity of levofloxacin was most similar to that of ciprofloxacin, although the percentage of resistant strains was <1% overall. Gatifloxacin was the most active quinolone tested, with MICs 2- to 4-fold lower than those of ciprofloxacin or levofloxacin.

Susceptibility patterns among* H. influenzae *isolates. The highest percentage of amoxicillin-resistant *H. influenzae* strains (MIC, $\geq$4 μg/mL) was observed in the United States (31.5%), followed by Canada (27.0%) > the Asia-Pacific region (16.2%) > Latin America (12.5%) > Europe (11.8%) (table 2). Cefprozil, cefaclor, and loracarbef were the least active oral cephalosporins tested, especially in Canada and the United States (3.8%–9.4% resistance). Azithromycin was the most active (MIC_{90}, 1–2 μg/mL) among the macrolides tested, and no significant differences were observed between geographic areas. TMP-SMX activity was diminished (13.9%–30.8% resistant strains), with a sig-

Table 1. In vitro activity of 24 antimicrobial agents against 8252 respiratory tract isolates of *Streptococcus pneumoniae* collected in the SENTRY program (1997–1999) in the Western Hemisphere, Europe, and the Asia-Pacific region.

Antimicrobial agent	United States ($n = 4193$)			Canada ($n = 887$)			Latin America ($n = 948$)			Europe ($n = 1478$)			Asia-Pacific ($n = 746$)		
	MIC_{50}	MIC_{90}	% R	MIC_{50}	MIC_{90}	% R	MIC_{50}	MIC_{90}	% R	MIC_{50}	MIC_{90}	% R	MIC_{50}	MIC_{90}	% R
Penicillin	0.03	2	14.0	0.03	1	6.8	≤0.03	2	11.7	≤0.03	2	10.4	≤0.03	2	17.8
Amoxicillin	≤0.06	2	3.2	≤0.06	2	1.0	≤0.06	1	0.5	≤0.06	1	1.7	≤0.06	2	0.0
Amoxicillin-clavulanate	≤0.25	2	2.8	≤0.25	2	0.8	≤0.25	2	0.4	≤0.25	2	1.6	≤0.25	2	0.0
Cefaclor	1	>32	26.2	1	8	11.3	1	>32	21.7	1	>32	21.1	1	>32	35.7
Loracarbef	1	>32	21.3	1	>32	14.3	1	>32	15.7	1	>32	17.4	1	>32	28.6
Cefprozil	0.5	8	16.3	0.25	4	9.0	0.25	8	13.3	0.25	8	12.1	0.25	8	19.5
Cefixime	0.5	>4	—[a]	0.25	>4	—[a]	0.5	>4	—[a]	0.25	>4	—[a]	1	>4	—[a]
Cefuroxime	≤0.06	4	21.8	≤0.06	2	9.2	≤0.06	4	15.8	≤0.06	4	16.6	≤0.06	8	29.1
Cefpodoxime	0.06	2	16.1	≤0.03	1	9.2	≤0.03	2	12.6	≤0.03	2	11.1	0.06	2	22.9
Cefepime	≤0.06	1	3.9	≤0.06	0.5	2.3	≤0.06	1	2.5	≤0.06	1	3.2	≤0.06	1	2.7
Cefotaxime	0.03	1	3.7	0.03	0.5	2.7	0.03	1	1.8	0.015	1	2.6	0.03	1	3.7
Erythromycin	≤0.25	4	17.7	≤0.25	1	10.4	≤0.25	1	10.5	≤0.25	>32	20.4	≤0.25	>32	38.6
Azithromycin	≤0.12	2	13.6	≤0.12	1	8.1	≤0.12	0.5	8.6	≤0.12	>16	17.8	≤0.12	>16	36.7
Clarithromycin	≤0.25	2	16.0	≤0.25	0.5	9.6	≤0.25	0.5	9.8	≤0.25	>32	18.2	≤0.25	>32	38.7
Clindamycin	≤0.06	0.25	4.7	≤0.06	0.25	3.7	≤0.06	0.25	5.0	≤0.06	>8	15.4	0.12	>8	20.0
Quinupristin-dalfopristin	0.5	0.5	0.0	0.5	0.5	0.0	0.5	0.5	0.1	0.5	1	0.0	0.5	1	0.0
Chloramphenicol	≤2	4	6.4	≤2	4	4.2	≤2	4	4.8	≤2	4	10.0	4	16	15.8
Tetracycline	≤2	16	12.0	≤2	4	9.6	≤2	≤2	19.6	≤2	>16	24.0	≤2	>16	41.7
Trimethoprim-sulfamethoxazole	≤0.5	4	19.8	≤0.25	4	14.4	≤0.5	4	23.8	≤0.25	4	15.2	0.5	8	27.3
Rifampin	≤1	≤1	0.3	≤1	≤1	0.2	≤1	≤1	2.5	≤1	≤1	0.8	≤1	≤1	0.6
Ciprofloxacin	1	2	—[b]	1	2	—[b]	1	2	—[b]	1	2	—[b]	1	2	—[b]
Levofloxacin	1	2	0.4	1	2	0.4	1	1	0.1	1	1	0.1	1	1	0.7
Gatifloxacin	0.25	0.5	0.2	0.25	0.5	0.2	0.25	0.5	0.1	0.25	0.5	1.0	0.25	0.25	0.4
Vancomycin	0.25	0.5	0.0	0.25	0.5	0.0	0.25	0.5	0.0	0.25	0.5	0.1	0.5	0.5	0.3

NOTE. % R, percentage of strains resistant by National Committee for Clinical Laboratory Standards (NCCLS) criteria [38, 39]; TMP-SMX, trimethoprim-sulfamethoxazole.

[a] Susceptibility indicated by the penicillin test results [39].

[b] No criteria were published in the NCCLS documents.

Table 2. In vitro activity of 24 antimicrobial agents against 6242 respiratory tract isolates of *Haemophilus influenzae* collected in the SENTRY program (1997–1999) in the Western Hemisphere, Europe, and the Asia-Pacific region.

Antimicrobial agent	United States ($n = 3116$)			Canada ($n = 748$)			Latin America ($n = 526$)			Europe ($n = 1283$)			Asia-Pacific region ($n = 569$)		
	MIC_{50}	MIC_{90}	% R	MIC_{50}	MIC_{90}	% R	MIC_{50}	MIC_{90}	% R	MIC_{50}	MIC_{90}	% R	MIC_{50}	MIC_{90}	% R
Penicillin	0.5	>16	—[a]	0.5	>16	—[a]	0.5	>4	—[a]	0.25	>4	—[a]	0.5	>4	—[a]
Amoxicillin	0.5	>8	31.5	0.5	>8	27.0	0.5	>8	12.5	0.5	8	11.8	0.5	>8	16.2
Amoxicillin-clavulanate	0.5	2	0.3	0.5	>8	0.3	0.5	1	0.0	0.5	1	0.2	0.5	1	0.0
Cefaclor	4	16	9.4	2	16	8.4	2	8	1.2	1	8	1.1	4	16	2.3
Loracarbef	2	8	3.8	2	8	3.6	2	4	0.7	1	4	0.2	2	8	0.9
Cefprozil	4	16	10.0	4	16	10.0	2	8	1.1	2	8	1.0	4	8	1.4
Cefixime	≤0.03	0.06	0.1	≤0.03	0.06	0.0	≤0.03	0.06	0.0	≤0.03	0.06	0.0	≤0.03	0.12	0.0
Cefuroxime	1	2	0.6	1	4	0.9	1	2	0.0	0.5	2	0.0	1	4	0.4
Cefpodoxime	0.06	0.12	0.1	0.06	0.25	0.0	0.06	0.12	0.0	0.06	0.12	0.0	0.06	0.25	0.5
Cefepime	≤0.06	0.25	0.1	0.12	0.25	0.1	≤0.06	0.25	0.4	0.12	0.25	0.1	0.12	0.12	0.0
Cefotaxime	0.015	0.03	0.0	0.015	0.03	0.0	0.015	0.03	0.0	0.015	0.03	0.1	0.015	0.03	0.0
Erythromycin	4	8	—[a]	4	8	—[a]	4	8	—[a]	4	4	—[a]	4	4	—[a]
Azithromycin	1	2	0.5	1	2	0.5	1	2	0.4	1	2	0.2	0.5	1	0.2
Clarithromycin	8	16	2.1	8	16	2.0	8	16	1.0	4	8	0.9	8	8	0.2
Clindamycin	8	>8	—[a]	8	>8	—[a]	4	>8	—[a]	4	8	—[a]	4	8	—[a]
Quinupristin-dalfopristin	4	8	—[a]	4	8	—[a]	>2	>2	—[a]	2	4	—[a]	>2	4	—[a]
Chloramphenicol	≤2	≤2	0.4	≤2	≤2	0.5	≤2	≤2	1.7	≤2	≤2	1.6	≤2	≤2	2.6
Tetracycline	≤2	≤2	0.7	≤2	≤2	0.8	≤2	≤2	1.5	≤2	≤2	2.6	≤2	≤2	2.6
Trimethoprim-sulfamethoxazole	≤0.5	4	14.6	≤0.25	8	18.6	0.5	8	30.8	≤0.25	>4	17.8	≤0.5	>4	13.9
Rifampin	≤1	≤1	0.0	≤1	≤1	0.0	≤1	≤1	0.4	≤1	≤1	0.0	≤1	≤1	0.5
Ciprofloxacin	≤0.015	≤0.015	0.1	≤0.015	≤0.015	0.0	≤0.015	≤0.015	0.0	≤0.015	≤0.015	0.0	≤0.015	≤0.015	0.0
Levofloxacin	≤0.5	≤0.5	0.0	≤0.5	≤0.5	0.0	≤0.5	≤0.5	0.0	≤0.5	≤0.5	0.0	≤0.5	≤0.5	0.0
Gatifloxacin	≤0.03	≤0.03	0.0	≤0.03	≤0.03	0.0	≤0.03	≤0.03	0.0	≤0.03	≤0.03	0.0	≤0.03	≤0.03	0.0
Vancomycin	>16	>16	—[a]	>16	>16	—[a]	>16	>16	—[a]	>16	>16	—[a]	>16	>16	—[a]

NOTE. % R, percentage of strains resistant by National Committee for Clinical Laboratory Standards (NCCLS) criteria [38, 39].

[a] No criteria were published in NCCLS documents.

Table 3. In vitro activity of 24 antimicrobial agents against 2815 respiratory tract isolates of *Moraxella catarrhalis* collected in the SENTRY program (1997–1999) in the Western Hemisphere, Europe, and the Asia-Pacific region.

Antimicrobial agent	United States ($n = 1411$)			Canada ($n = 365$)			Latin America ($n = 265$)			Europe ($n = 520$)			Asia-Pacific region ($n = 254$)		
	MIC_{50}	MIC_{90}	% R	MIC_{50}	MIC_{90}	% R	MIC_{50}	MIC_{90}	% R	MIC_{50}	MIC_{90}	% R	MIC_{50}	MIC_{90}	% R
Penicillin	>4	16	96.0	>4	>4	96.9	4	>4	97.6	4	8	95.3	>4	>4	97.0
Amoxicillin-clavulanate	≤0.25	0.25	0.1	≤0.25	0.25	0.0	≤0.25	0.25	0.4	≤0.25	0.25	0.0	≤0.25	≤0.25	0.0
Cefaclor	1	2	0.1	0.5	2	0.0	0.5	2	0.0	0.5	1	0.0	1	4	2.6
Loracarbef	1	2	0.0	1	2	0.0	0.5	2	0.0	1	2	0.0	1	4	0.0
Cefprozil	2	8	0.8	2	8	0.6	2	4	0.0	2	4	0.0	2	8	3.4
Cefixime	0.25	0.5	0.3	0.25	0.5	0.0	0.25	0.25	0.0	0.12	0.25	0.0	0.25	0.25	0.0
Cefuroxime	1	2	0.1	1	2	0.0	1	2	0.0	1	2	0.2	2	4	0.0
Cefpodoxime	0.5	1	0.1	0.5	1	0.0	0.5	1	0.0	0.5	1	0.0	0.5	1	0.0
Cefepime	0.5	2	0.0	0.5	2	0.0	0.5	2	0.0	0.5	2	0.0	0.5	2	0.0
Cefotaxime	0.5	1	0.0	0.5	0.5	0.0	0.25	0.5	0.0	0.25	0.5	0.0	0.5	1	0.0
Erythromycin	≤0.25	0.5	0.4	≤0.25	0.5	0.0	≤0.25	0.5	2.8	≤0.25	≤0.25	0.8	≤0.25	0.5	0.0
Azithromycin	≤0.12	≤0.12	0.1	≤0.12	≤0.12	0.0	≤0.12	≤0.12	0.4	≤0.12	≤0.12	0.2	≤0.12	≤0.12	0.0
Clarithromycin	≤0.25	≤0.25	0.4	≤0.25	≤0.25	0.0	≤0.25	≤0.25	0.4	≤0.25	≤0.25	0.8	≤0.25	≤0.25	0.0
Clindamycin	2	4	96.8	2	4	98.6	2	4	96.3	1	2	95.3	2	>2	99.6
Quinupristin-dalfopristin	0.25	0.5	0.4	0.5	0.5	0.3	0.5	0.5	0.8	0.25	0.5	0.6	0.5	0.5	0.0
Chloramphenicol	≤2	≤2	0.0	≤2	≤2	0.0	≤2	≤2	0.0	≤2	≤2	0.1	≤2	4	0.0
Tetracycline	≤2	≤2	0.1	≤2	≤2	0.0	≤2	≤2	0.4	≤2	≤2	0.6	≤2	≤2	2.4
Trimethoprim-sulfamethoxazole	≤0.25	0.5	0.9	≤0.25	0.5	1.1	≤0.5	1	2.6	≤0.25	0.5	0.8	≤0.5	0.5	0.8
Rifampin	≤1	≤1	0.1	≤1	≤1	0.0	≤1	≤1	0.0	≤1	≤1	0.0	≤1	≤1	0.0
Ciprofloxacin	0.03	0.06	0.1	0.03	0.03	0.0	0.03	0.06	0.0	0.03	0.03	0.0	0.03	0.06	0.0
Levofloxacin	≤0.5	≤0.5	0.1	≤0.5	≤0.5	0.0	≤0.5	≤0.5	0.0	≤0.5	≤0.5	0.0	≤0.03	0.06	0.0
Gatifloxacin	≤0.03	≤0.03	0.1	≤0.03	≤0.03	0.0	≤0.03	0.06	0.0	≤0.03	≤0.03	0.0	≤0.03	≤0.03	0.0
Gentamicin	≤1	≤1	0.0	≤1	≤1	0.0	≤1	≤1	0.0	≤1	≤1	0.0	≤1	≤1	0.0
Vancomycin	>16	>16	99.2	>16	>16	99.7	>16	>16	100.0	>16	>16	98.6	>16	>16	100.0

NOTE. % R, percentage of strains resistant by National Committee for Clinical Laboratory Standards [38, 39] criteria for staphylococci (gram-positive-spectrum drugs) and for Enterobacteriaceae (broad-spectrum agents).

nificantly higher rate of resistance in Latin America. Only 0.5% and 0.4% of isolates from the Asia-Pacific region and Latin America, respectively, were resistant to rifampin. Less than 3.0% of strains were resistant to chloramphenicol and tetracycline; the highest percentage of resistance was observed in the Asia-Pacific region. Ciprofloxacin, levofloxacin, and gatifloxacin all had excellent activity (MIC_{90}, ≤0.015 to ≤0.5 μg/mL) against *H. influenzae* in all geographic areas studied, and only 0.1% of strains in the United States were resistant to ciprofloxacin.

Susceptibility patterns among* M. catarrhalis *isolates. The highest percentage of *M. catarrhalis* isolates (among the 2815 collected) that were resistant to penicillin, on the basis of MICs and β-lactamase production, was observed in Latin America (97.6%; table 3). Amoxicillin-clavulanate was active against almost all isolates of this microorganism (MIC_{90}, 0.25 μg/mL; 0.0%–0.4% resistance). Among the cephalosporins tested, cefaclor and cefprozil were the least active, showing rates of resistance ranging from 0% in Latin America to 2.6%–3.4% in the Asia-Pacific region. The activity of the other drugs tested (macrolides, quinolones, chloramphenicol, tetracycline, TMP-SMX, and rifampin) was excellent; <1% of strains were resistant in all geographic areas, except for TMP-SMX (2.6% of strains were resistant in Latin America) and tetracycline (2.4% of strains were resistant in the Asia-Pacific region).

***Co-resistance patterns in* S. pneumoniae.** Table 4 shows the rates of resistance to erythromycin, clindamycin, chloramphenicol, tetracycline, and TMP-SMX among *S. pneumoniae* isolates, according to penicillin-susceptibility categories and geographic locations. There was a clear relationship between penicillin category and the activity of these selected antimicrobials in all regions. In all cases, resistance to these agents was more common among strains intermediately susceptible to penicillin than among penicillin-susceptible strains, and it was even more common among highly penicillin-resistant organisms.

Resistance trends during the study interval. From 1997 to 1999, the rates of resistance of *S. pneumoniae* to selected representatives of 7 drug classes (table 5) remained relatively stable, although there was a noteworthy increase ($P < .05$) in resistance to some antimicrobials: penicillin (Europe); erythromycin, clindamycin, chloramphenicol, tetracycline, and TMP-SMX (United States); erythromycin, clindamycin, chloramphenicol, and TMP-SMX (Europe); and erythromycin, clindamycin, and tetracycline (the Asia-Pacific region). With regard to *H. influenzae* (table 6), the only modest change in susceptibility was noted in Canada and the United States, where a reduction in resistance to cefaclor was seen (from 11.6% in 1997 to 3.1% in 1999; data not shown). All other drugs selected from the 6 antimicrobial classes represented in table 6 showed a stable pattern of potency and spectrum. The same situation was observed with regard to *M. catarrhalis* isolates, among which there was a decrease in resistance to TMP-SMX (from 5.4% in 1997 to 0.0% in 1999), in Latin America only (data not shown).

Influence of infection site on resistance patterns. There were significant differences in the susceptibility patterns of *S. pneumoniae* strains isolated from blood and the respiratory tract (table 7). In many cases these differences were limited, but in some geographic areas (the Asia-Pacific region) the percentage of resistant *S. pneumoniae* isolates from the respiratory tract was markedly higher than that of isolates from blood. For example, rates of resistance to erythromycin and tetracycline were >40% among respiratory isolates but 18%–28% among bloodstream isolates. Isolates from hospitalized patients with pneumonia were equally resistant to or more resistant than the isolates from patients with community-acquired respiratory tract infections. The main exception was the resistance to all studied drugs (table 7) that was seen in the United States. The greatest resistances among bloodstream isolates of *S. pneumoniae* were found in the Asia-Pacific region, followed by Europe > Latin America > North America. The regional rank order of resistances among respiratory tract isolates was identical to that listed above.

With regard to *H. influenzae* (table 8), the most important differences were observed in Canada (8.3% of bacteria isolated from blood samples were resistant to cefuroxime) and Latin America (10% of bacteria isolated from blood samples were resistant to chloramphenicol and tetracycline); in comparison, <2% of the isolates from the respiratory tract were resistant to these drugs. In each case, the number of isolates was <50 (data not shown). In Europe, higher rates of resistance to TMP-SMX were observed in bloodstream isolates (38.7%) than in respiratory tract isolates (11%–18%). Among the isolates from the respiratory tract, the biggest differences between strains from hospitalized and ambulatory patients were observed in the rates of resistance to TMP-SMX (4% vs. 18%, respectively) in the Asia-Pacific region and in Europe (11% vs. 18%).

With regard to *M. catarrhalis,* the most important differences in resistance between bloodstream and respiratory tract isolates were observed with TMP-SMX in Canada and tetracycline in the Asia-Pacific region. However, the low number of *M. catarrhalis* isolates studied, especially from blood cultures, prevents firm comparison of the susceptibility patterns by site of infection or geography (data not shown).

β-lactamase production rates. Table 9 shows rates of β-lactamase production by *H. influenzae* and *M. catarrhalis* isolates, classified by year and geographic region. For this study period, the percentage of β-lactamase-producing *H. influenzae* isolates varied from 12% to 34%. The highest rates of these β-lactamase-positive strains overall were observed in the United States (33%) and Canada (29%), but in the latter country a decrease from 31% in 1997 to 22% in 1999 was documented. Rates lower than 20% were routinely found in Latin America,

Table 4. Relationship between rates of resistance to 5 antimicrobial agents among *Streptococcus pneumoniae* isolates in the Western Hemisphere, Europe, and the Asia-Pacific region, listed according to penicillin-susceptibility category (SENTRY program, 1997–1999).

	Resistant isolates, %														
	United States			Canada			Latin America			Europe			Asia-Pacific		
Antimicrobial agent	PenS ($n = 2756$)	PenI ($n = 848$)	PenR ($n = 589$)	PenS ($n = 682$)	PenI ($n = 145$)	PenR ($n = 60$)	PenS ($n = 630$)	PenI ($n = 207$)	PenR ($n = 111$)	PenS ($n = 1025$)	PenI ($n = 300$)	PenR ($n = 153$)	PenS ($n = 465$)	PenI ($n = 148$)	PenR ($n = 133$)
Erythromycin	4	32	61	7	19	33	4	20	27	10	40	52	22	58	76
Clindamycin	<1	10	17	2	8	8	2	13	9	6	31	47	10	38	34
Chloramphenicol	<1	9	31	2	6	32	2	6	19	3	17	43	6	20	45
Tetracycline	3	19	44	5	21	40	18	26	19	15	40	52	24	63	79
TMP-SMX	6	37	78	6	33	82	13	44	87	6	32	67	13	38	82

NOTE. PenS, penicillin susceptible (MIC, $\leq$0.06 μg/mL); PenI, intermediately susceptible to penicillin (MIC, 0.12–1 μg/mL); PenR, penicillin resistant (MIC, $\geq$2 μg/mL) [38, 39]; TMP-SMX, trimethoprim-sulfamethoxazole.

Table 5. Rates of resistance to representatives of 7 antimicrobial-agent classes among clinical isolates of *Streptococcus pneumoniae* in the Western Hemisphere, Europe, and the Asia-Pacific region (SENTRY program, 1997–1999).

	Resistant isolates, %[a]													
	United States			Canada			Latin America			Europe			Asia-Pacific	
Antimicrobial agent	1997 ($n = 1357$)	1998 ($n = 1398$)	1999 ($n = 1438$)	1997 ($n = 360$)	1998 ($n = 265$)	1999 ($n = 262$)	1997 ($n = 241$)	1998 ($n = 312$)	1999 ($n = 395$)	1997 ($n = 513$)	1998 ($n = 675$)	1999 ($n = 290$)	1998 ($n = 412$)	1999 ($n = 34$)
Penicillin	14	13	15	8	8	4	10	10	14	6	9	22[b]	20	15
Cefotaxime	4	3	5	3	5	0	<1	2	3	1	2	8[b]	5	2
Erythromycin	13	17	23[b]	9	11	11	9	13	10	15	22	25[b]	34	45[b]
Clindamycin	3	4	7[b]	4	3	3	6	7	3	12	16	18[b]	18	23[b]
Chloramphenicol	4	5	9[b]	6	1	5	5	5	4	8	9	16[b]	18	14
Tetracycline	9	11	16[b]	12	8	8	17	24	18	24	24	25	39	45[b]
TMP-SMX	19	19	29[b]	16	16	14	32	18	27	13	12	38[b]	37	22

NOTE. TMP-SMX, trimethoprim-sulfamethoxazole.

[a] Resistance defined by National Committee for Clinical Laboratory Standards criteria [38, 39].

[b] Significant ($P < .05$) increases in resistance over 2- or 3-year study interval.

Table 6. Rates of resistance to representatives of 6 antimicrobial-agent classes among clinical isolates of *Haemophilus influenzae* in the Western Hemisphere, Europe, and the Asia-Pacific region (SENTRY program, 1997–1999).

	Resistant isolates, %[a]													
	United States			Canada			Latin America			Europe			Asia-Pacific	
Antimicrobial agent	1997 ($n = 1099$)	1998 ($n = 1116$)	1999 ($n = 901$)	1997 ($n = 328$)	1998 ($n = 224$)	1999 ($n = 196$)	1997 ($n = 81$)	1998 ($n = 280$)	1999 ($n = 165$)	1997 ($n = 443$)	1998 ($n = 629$)	1999 ($n = 211$)	1998 ($n = 348$)	1999 ($n = 221$)
Amoxicillin-clavulanate	<1	<1	0	<1	0	0	0	0	0	<1	0	<1	0	0
Cefuroxime	1	<1	<1	2	<1	0	0	0	0	0	0	0	0	<1
Chloramphenicol	<1	<1	<1	<1	0	1	3	2	1	1	2	<1	2	3
Tetracyclines	<1	<1	<1	1	0	1	1	2	1	3	2	2	3	3
TMP-SMX	16	14	14	18	15	19	31	31	30	19	16	19	16	11
Ciprofloxacin[b]	<1	<1	0	0	0	0	0	0	0	0	0	0	0	0

NOTE. TMP-SMX, trimethoprim-sulfamethoxazole.

[a] Resistance defined by National Committee for Clinical Laboratory Standards criteria [38, 39].

[b] Additional strains with gyrase/topoisomerase mutations were identified for which MICs were in the susceptible range (≤ 1 μg/mL).

Table 7. Rates of resistance to representatives of 7 antimicrobial-agent classes among *Streptococcus pneumoniae* isolates from patients with bloodstream or respiratory tract infections in the Western Hemisphere, Europe, and the Asia-Pacific region (SENTRY program, 1997–1999).

	Resistant isolates, %													
	United States			Canada			Latin America			Europe			Asia-Pacific	
Antimicrobial agent	BSI ($n = 863$)	CARTI ($n = 2796$)	LRTI ($n = 534$)	BSI ($n = 217$)	CARTI ($n = 567$)	LRTI ($n = 103$)	BSI ($n = 203$)	CARTI ($n = 666$)	LRTI ($n = 79$)	BSI ($n = 264$)	CARTI ($n = 1064$)	LRTI ($n = 150$)	BSI ($n = 142$)	CARTI ($n = 566$)
Penicillin	10	16	9	6	7	10	11	12	13	10	10	17	13	18
Cefotaxime	2	4	2	2	2	7	2	2	0	2	3	3	4	4
Erythromycin	10	20	16	9	10	16	7	11	14	23	19	27	28	41
Clindamycin	2	6	5	3	3	9	3	6	6	18	14	20	11	23
Chloramphenicol	3	8	5	2	4	8	1	6	6	9	10	15	8	17
Tetracycline	6	14	10	6	10	17	21	20	15	23	23	32	18	47
TMP-SMX	18	24	19	13	16	18	22	31	25	17	18	19	28	30

NOTE. BSI, bloodstream infection; CARTI, community-acquired respiratory tract infection; LRTI, pneumonia in hospitalized patient (lower respiratory tract infection); TMP-SMX, trimethoprim-sulfamethoxazole.

Table 8. Rates of resistance to 7 antimicrobial agents among *Haemophilus influenzae* isolates from patients with community-acquired respiratory tract infections or pneumonia in the Western Hemisphere, Europe, and the Asia-Pacific region (SENTRY program, 1997–1999).

	Resistant isolates, %								
	United States		Canada		Latin America	Europe		Asia-Pacific	
Antimicrobial agent	CARTI ($n = 2648$)	LRTI ($n = 434$)	CARTI ($n = 625$)	LRTI ($n = 111$)	CARTI ($n = 508$)	CARTI ($n = 1161$)	LRTI ($n = 91$)	CARTI ($n = 513$)	LRTI ($n = 53$)
Amoxicillin-clavulanate	<1	1	<1	0	0	<1	0	0	0
Cefuroxime	<1	<1	<1	<1	0	0	0	<1	0
Cefotaxime	0	0	0	0	0	<1	0	0	0
Chloramphenicol	<1	<1	<1	0	2	1	3	3	0
Tetracycline	<1	<1	1	0	1	2	3	3	0
TMP-SMX	15	13	17	19	31	18	11	15	4
Gatifloxacin	0	0	0	0	0	0	0	0	0

NOTE. CARTI, community-acquired respiratory tract infection; LRTI, lower respiratory tract infection (pneumonia in hospitalized patient); TMP-SMX, trimethoprim-sulfamethoxazole.

Europe, and the Asia-Pacific region. The percentage of β-lactamase-producing *M. catarrhalis* isolates varied from 92% to 99% during the study period and across the 5 geographic areas studied. No important variation was observed during the study period in the 5 regions.

DISCUSSION

The SENTRY Antimicrobial Surveillance Program, begun in January 1997, was designed to monitor antimicrobial resistance trends of both nosocomial and community-acquired pathogens over broad geographic areas, using validated reference identification and susceptibility testing methods at designated central laboratories [14, 16, 22, 34, 36, 40]. The objective of this investigation was to study the susceptibility of blood culture and respiratory tract clinical isolates of *S. pneumoniae, H. influenzae,* and *M. catarrhalis* from 5 geographic regions: the United States, Canada, Europe, Latin America, and the Asia- Pacific region.

Resistance to penicillin (MIC, ⩾2 μg/mL) was noted among US (14.0%), Canadian (6.8%), Latin American (11.7%), European (10.4%), and Asia-Pacific region (17.8%) isolates of *S. pneumoniae.* The highest rates of penicillin resistance among clinical isolates of *S. pneumoniae* were noted among the isolates from patients with pneumonia, especially in the Asia-Pacific region (28.9%) and Europe (16.7%). Only in the United States was the percentage of resistance higher among isolates from patients with community-acquired respiratory tract infections than among isolates from patients with pneumonia. An important increase in pneumococcal resistance was observed among clinical isolates from Europe and Latin America in 1999 (22.4% and 14.4%, respectively) in relation to 1998 (8.6% and 9.9%) and 1997 (5.8% and 9.5%); these data show the escalating problem of penicillin resistance. However, a slight decrease in rates of resistance was noted in Canada and the Asia-Pacific region from 1998 (8.3% and 20.4%, respectively) to 1999 (3.8% and 14.7%). Of the orally administered agents, the activity of cephalosporins was particularly poor (26.2% for cefaclor), but the rate of resistance to cefotaxime and cefepime was not as high (⩽3.9%).

Except for ciprofloxacin, nearly all *S. pneumoniae* strains tested were susceptible to fluoroquinolones, such as levofloxacin (⩽0.7% resistant). Gatifloxacin was 2- to 4-fold more

Table 9. β-lactamase production by clinical isolates of *Haemophilus influenzae* and *Moraxella catarrhalis* in the Western Hemisphere, Europe, and the Asia-Pacific region (SENTRY program, 1997–1999).

	H. influenzae		*M. catarrhalis*	
Country or region, year	No. tested	β-lactamase-positive, %	No. tested	β-lactamase-positive, %
United States				
1997	1099	34	452	92
1998	1116	33	448	95
1999	901	33	445	94
Canada				
1997	328	31	158	92
1998	224	29	97	97
1999	196	22	99	94
Latin America				
1997	81	16	56	96
1998	280	12	103	94
1999	165	16	62	98
Europe				
1999	211	18	91	99
Asia-Pacific				
1998	359	19	125	97
1999	229	17	115	96

active than levofloxacin, as has been demonstrated elsewhere [22]. Resistance of *S. pneumoniae* to newer fluoroquinolones has been demonstrated to be due to a *parC* and *gyrA* mutation [22]. The incidence of infection with fluoroquinolone-resistant pneumococci has increased, and these organisms have been well documented by Chen et al. [41] in North America. This finding was supported by detailed analysis in the SENTRY program, in which a 3- to 4-fold increase in levofloxacin resistance rates was detected between 1997–1998 and 1999 [42]. Increased resistance to macrolides (erythromycin, azithromycin, and clarithromycin), tetracyclines, and TMP-SMX was also observed in this study and elsewhere [41, 42].

Vancomycin resistance in pneumococcal isolates has rarely been reported [12]. In the SENTRY program, 0.3% of isolates from the Asia-Pacific region and 0.1% of isolates from Europe were reproducibly nonsusceptible to vancomycin, according to the current NCCLS breakpoint (MICs were 2 or 4 μg/mL) [38, 39]. These findings emphasize the need for surveillance studies of glycopeptides in *S. pneumoniae,* but the clinical relevance of these modestly elevated vancomycin MICs remains unclear. Quinupristin-dalfopristin, as in other studies [14], showed near-complete activity against *S. pneumoniae:* only 0.1% of strains were nonsusceptible (MIC, 2 μg/mL).

A high rate of resistance to macrolides was observed (10.4%–38.6% against erythromycin), and there were no important differences in the activity of newer agents such as azithromycin and clarithromycin. Resistance to clindamycin was especially high in Europe (15.4%) and in the Asia-Pacific region (20.0%), indicating a greater proportion of MLS_B resistance *(erm)*. High rates of resistance to chloramphenicol, tetracycline, and TMP-SMX were noted in all 5 of the geographic regions that were studied. It is interesting that rates of resistance to clindamycin, chloramphenicol, tetracycline, and TMP-SMX appear to have changed little, at least in the United States and Canada, since 1996 [2, 14].

Co-resistance (to erythromycin, clindamycin, chloramphenicol, tetracycline, and TMP-SMX) was higher among clinical isolates of *S. pneumoniae* that were intermediately susceptible or highly resistant to penicillin, a finding that confirms reports from other investigators [14]. Since no common mechanism of resistance has been demonstrated between penicillin and these other antimicrobial classes, this fact probably reflects the pressure of broad-based antimicrobial use on *S. pneumoniae.* Of note are the high rates of resistance to these antimicrobial agents among penicillin-susceptible *S. pneumoniae* strains, especially in the Asia-Pacific region, Europe (erythromycin, tetracycline), and Latin America (tetracycline, TMP-SMX), where these "essential drugs" (so termed by the World Health Organization) have been widely used.

Ninety clinical isolates of *H. influenzae* were recovered from blood samples, as were 24 clinical isolates of *M. catarrhalis.* Although in some regions the number of bloodstream isolates of these microorganisms was not high, this study yielded one of the highest number of isolates from this anatomic source. The percentage of β-lactamase-producing *M. catarrhalis* strains has increased over the years to include nearly all isolates [11, 24–27, 35]. In this survey, rates of β-lactamase-producing *M. catarrhalis* did not change during the study period. However, important regional differences in β-lactamase production in *H. influenzae* (highest in the United States) were observed, but the rates of resistance to ampicillin [11, 23–25, 27, 41] were stable, with no important differences during the study period. The other β-lactams studied have, in general, potent activity against *H. influenzae* (except cefprozil, cefaclor, and loracarbef), which reflects the resistance of these drugs to the TEM β-lactamase in *H. influenzae* [25]. The high resistance to TMP-SMX (30.8%) observed in Latin America limits the use of this "essential" compound.

The macrolides (except erythromycin), chloramphenicol, tetracycline, rifampin, and the fluoroquinolones showed continued good activity against *H. influenzae.* All the antimicrobials tested, except TMP-SMX, have good activity and spectrum coverage against *M. catarrhalis.* With some minor exceptions, there were no important differences in the susceptibility of *H. influenzae* or *M. catarrhalis* with regard to the year of isolation, the isolate-yielding sample, and the infection site.

These data confirm some significant regional differences in the antimicrobial susceptibility of *S. pneumoniae, H. influenzae,* and *M. catarrhalis* and establish the widespread nature and increasing prevalence of antimicrobial resistance in some of these microorganisms [6, 19, 25, 35, 36, 43–45]. These results from the SENTRY program also confirm previous observations regarding the higher, emerging rates of resistance in *S. pneumoniae* worldwide. In addition, the findings emphasize the importance of antimicrobial surveillance programs for guiding empirical therapy and for focusing interventional control of antimicrobial resistance in distinct geographic areas, hospitals, and services, and they illustrate the need for new antimicrobial agents and vaccines [1, 43].

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