ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, June 2003, p. 1867–1874 Vol. 47, No. 6
0066-4804/03/$08.00+0 DOI: 10.1128/AAC.47.6.1867–1874.2003

Antimicrobial Resistance in Respiratory Tract *Streptococcus pneumoniae* Isolates: Results of the Canadian Respiratory Organism Susceptibility Study, 1997 to 2002

George G. Zhanel,[1,2,3] Lorraine Palatnick,[3] Kimberly A. Nichol,[1,3] Tracy Bellyou,[3] Don E. Low,[4] and Daryl J. Hoban[1,3]*

Department of Medical Microbiology, Faculty of Medicine, University of Manitoba,[1] and Departments of Medicine[2] and Clinical Microbiology,[3] Health Sciences Centre, Winnipeg, Manitoba, and Mount Sinai Hospital, Toronto, Ontario,[4] Canada

Received 6 September 2002/Returned for modification 23 January 2003/Accepted 26 February 2003

A total of 6,991 unique patient isolates of *Streptococcus pneumoniae* were collected from October 1997 to June 2002 from 25 medical centers in 9 of the 10 Canadian provinces. Among these isolates, 20.2% were penicillin nonsusceptible, with 14.6% being penicillin intermediate (MIC, 0.12 to 1 μg/ml) and 5.6% being penicillin resistant (MIC, ≥2 μg/ml). The proportion of high-level penicillin-resistant *S. pneumoniae* isolates increased from 2.4 to 13.8% over the last 3 years of the study, and the proportion of multidrug-resistant *S. pneumoniae* isolates increased from 2.7 to 8.8% over the 5-year period. Resistant rates (intermediate and resistant) among non-β-lactam agents were as follows: macrolides, 9.6 to 9.9%; clindamycin, 3.8%; doxycycline, 5.5%; chloramphenicol, 3.9%; and trimethoprim-sulfamethoxazole, 19.0%. Rates of resistance to non-β-lactam agents were higher among penicillin-resistant strains than among penicillin-susceptible strains. No resistance to vancomycin or linezolid was observed; however, 0.1% intermediate resistance to quinupristin-dalfopristin was observed. The rate of macrolide resistance (intermediate and resistant) increased from 7.9 to 11.1% over the 5 years. For the fluoroquinolones, the order of activity based on the MICs at which 50% of isolates are inhibited (MIC_{50}s) and the MIC_{90}s was gemifloxacin > clinafloxacin > trovafloxacin > moxifloxacin > grepafloxacin > gatifloxacin > levofloxacin > ciprofloxacin. The investigational compounds ABT-773 (MIC_{90}, 0.008 μg/ml), ABT-492 (MIC_{90}, 0.015 μg/ml), GAR-936 (tigecycline; MIC_{90}, 0.06 μg/ml), and BMS284756 (garenoxacin; MIC_{90}, 0.06 μg/ml) displayed excellent activities. Despite decreases in the rates of antibiotic consumption in Canada over the 5-year period, the rates of both high-level penicillin-resistant and multidrug-resistant *S. pneumoniae* isolates are increasing in Canada.

Streptococcus pneumoniae is a leading cause of morbidity and mortality worldwide (1, 14, 27, 32). It is the most common cause of community-acquired pneumonia, bacterial meningitis, and acute otitis media (2, 5, 10, 13, 25, 27, 32). Initially, all *S. pneumoniae* isolates were exquisitely susceptible to penicillin (MICs, ≤0.06 μg/ml) and β-lactams served as the treatment of choice for *S. pneumoniae* infections (2, 24, 27, 35). Beginning in the 1960s, however, resistance to penicillin and other agents began to be reported (2, 19, 24, 27). Reports of an increase in the prevalence of infections attributed to drug-resistant pneumococci appeared from a wide geographic area during the 1980s and, in particular, have appeared during the past 5 years, suggesting that drug resistance is spreading rapidly (1, 6, 11, 17, 21, 24, 30, 33, 34, 36, 37). Today, drug-resistant *S. pneumoniae* is recognized worldwide (16). In North America, recent surveys have shown an increase in the prevalence of resistance to penicillins from less than 5% before 1989 to more than 50% in 1999 (6, 11, 17, 23, 33, 34, 36, 37). In the United States in 1999 and 2000, of all *S. pneumoniae* isolates tested, 12.7% were intermediately resistant to penicillin (MICs, 0.12 to 1 μg/ml), while 21.5% were highly penicillin resistant (MICs, ≥2 μg/ml) (11). During 1997 in Canada, 14.8 and 6.4% of respiratory tract isolates of *S. pneumoniae* (n = 1,180) were penicillin intermediate and penicillin resistant, respectively (37). Most important and alarming is the finding that pneumococcal strains which are not susceptible (intermediate or resistant) to penicillin are more likely than penicillin-susceptible strains to be concomitantly resistant to other classes of antibiotics, including macrolides (6, 11, 17, 20, 33, 34, 36, 37).

The present report describes the results of the ongoing annual Canadian Respiratory Organism Susceptibility Study (CROSS) (37). This study included isolates from 25 medical centers from all regions of Canada participating from 1997 to 2002 inclusive. Use of isolates over a 5-year study period allows the evaluation of resistance rates over time.

MATERIALS AND METHODS

Between October 1997 and June 2002 a total of 6,991 unique patient *S. pneumoniae* isolates were collected from 25 medical centers in major population centers in 9 of the 10 provinces in Canada. Each study site was asked to collect and submit each year 100 *S. pneumoniae* isolates (from respiratory tract specimens only, one per patient) deemed significant by that study site. Isolate inclusion in this study was not dependent on patient age. All organisms were identified as *S. pneumoniae* at each site by the criteria used at the local site, and at the reference site, where indicated, the organisms were further identified by standard methodologies such as Gram staining characteristics, optochin disk testing, bile solubility, and colony characteristics on growth medium. At the study sites, the isolates were subcultured on 5% sheep blood agar plates and incubated for 24 h at 35°C in 5 to 10% CO_2 (37). Amies semisolid transport medium containing

* Corresponding author. Mailing address: Clinical Microbiology, Health Sciences Centre, MS673-820 Sherbrook St., Winnipeg, Manitoba R3A 1R9, Canada. Phone: (204) 787-1191. Fax: (204) 787-4699. E-mail: dhoban@hsc.mb.ca.

charcoal (Difco Laboratories, Detroit, Mich.) was then inoculated with the isolate and sent to the coordinating laboratory (Health Sciences Centre, Winnipeg, Manitoba, Canada), where the isolates were subcultured on 5% sheep blood agar and stocked in skim milk at −70°C.

Thirty-five antimicrobial agents (penicillin, amoxicillin-clavulanate, cefuroxime, cefprozil, cefixime, cefaclor, cefotaxime, ceftriaxone, imipenem, meropenem, erythromycin, azithromycin, clarithromycin, clindamycin, tetracycline, doxycycline, chloramphenicol, trimethoprim-sulfamethoxazole [TMP-SMX], vancomycin, quinupristin-dalfopristin, ciprofloxacin, levofloxacin, gatifloxacin, moxifloxacin, trovafloxacin, gemifloxacin, grepafloxacin, clinafloxacin, linezolid, telithromycin, ABT-773, ABT-492, ertapenem, BMS284756 [garenoxacin], GAR-936 [tigecycline]) were obtained as laboratory-grade powders from their respective manufacturers. Stock solutions were prepared and dilutions were made by the National Committee for Clinical Laboratory Standards (NCCLS) M7-A5 method (28). Following two subcultures from frozen stocks, the MICs of the antimicrobial agents for the isolates were determined by the NCCLS M7-A5 approved broth microdilution method (28, 29). Briefly, for the *S. pneumoniae* isolates, 96-well custom-designed microtiter plates containing doubling antibiotic dilutions in 100 μl of cation-adjusted Mueller-Hinton broth plus lysed horse blood (2 to 5%; vol/vol) per well were inoculated to achieve a final concentration of approximately 5×10^5 CFU/ml, and the plates were incubated in ambient air for 24 h prior to reading of the results. Colony counts were determined periodically to confirm the inocula. Quality control was performed every 2 weeks by using the following quality control organisms from the American Type Culture Collection (ATCC): *S. pneumoniae* ATCC 49619, *Staphylococcus aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, *Escherichia coli* ATCC 25922, and *Pseudomonas aeruginosa* ATCC 27853.

TABLE 1. Isolation of *S. pneumoniae* isolates from 1997 to 2002 by specimen source, service, gender, and age

Characteristic	1997–1998	1998–1999	1999–2000	2000–2001	2001–2002
No. of isolates	1,180	1,333	1,593	1,435	1,450
Specimen type (% of isolates)					
Sputum or BAL[a] specimen	90.1	90.5	90.0	92.3	91.0
Other[b]	9.9	9.5	10.0	7.7	9.0
Service (% of isolates)					
Inpatient	54.2	52.2	54.7	54.7	53.6
Outpatient	45.8	47.8	45.3	45.3	46.4
Gender (% of isolates)					
Female	39.8	39.2	40.4	38.8	39.2
Male	60.2	60.8	59.6	61.2	60.8
Age group (% of isolates)					
≤16 yr	22.0	22.0	24.5	18.6	21.5
17–64 yr	39.7	39.1	39.4	40.7	40.1
≥65 yr	38.3	38.9	36.1	40.7	38.4

[a] Sputum specimen, bronchoal veolar lavage (BAL) specimens, or endotracheal secretions.
[b] Middle ear fluid, sinus fluid, or conjunctival swabs.

RESULTS

The demographics of the patients whose isolates were included in CROSS are described in Table 1. The numbers of *S. pneumoniae* isolates recovered from respiratory sources varied from 1,180 to 1,593 per year over the 5-year study period. In each year of the study, ≥90% of *S. pneumoniae* isolates were isolated from sputum specimens, bronchoalveolar lavage specimens, or endotracheal secretions. Approximately 54 and 46% of the isolates submitted were obtained from inpatients and outpatients, respectively, and approximately 40 and 60% of the isolates submitted were from females and males, respectively. The breakdowns of the *S. pneumoniae* isolates submitted by age group were approximately 20% from individuals ≤16 years of age, 40% from individuals 17 to 64 years of age, and 40% from individuals ≥65 years of age. Table 1 indicates that the demographics of the patients from whom isolates were recovered did not change over the 5-year study period.

The in vitro activities of 35 antibiotics against 6,991 *S. pneumoniae* isolates are presented in Table 2. Only the new breakpoints of amoxicillin-clavulanate, as well as those of cephalosporins such as cefuroxime, cefprozil, cefaclor, cefotaxime, and ceftriaxone, for *S. pneumoniae* were used (29). Among the collection of 6,991 *S. pneumoniae* isolates, 20.2% were penicillin nonsusceptible, with 14.6% being penicillin intermediate (MICs, 0.12 to 1 μg/ml) and 5.6% being penicillin resistant (MICs, ≥2 μg/ml) (Table 2). Rates of resistance to amoxicillin-clavulanate were low among the penicillin-intermediate and -resistant isolates (0.8 and 0.1%, respectively). The activities of expanded-spectrum cephalosporins on the basis of the MICs at which 90% of isolates are inhibited (MIC_{90}s) were as follows: cefuroxime = cefprozil > cefixime > cefaclor. On the basis of the breakpoints, the lowest percentages of intermediate resistance and resistance occurred with cefprozil and cefuroxime (Table 2). Among all *S. pneumoniae* isolates tested, rates of intermediate and high-level resistance to broad-spectrum cephalosporins were 0.2 and 0.1%, respectively, for cefotaxime and 0.1 and 0%, respectively, for ceftriaxone. For carbapenems, imipenem demonstrated greater activity than meropenem, on the basis of the MIC_{90}s.

When isolates were grouped according to penicillin susceptibility, the highest rates of resistance to all β-lactam and β-lactam-like agents including penicillins, cephalosporins, and carbapenems occurred among the penicillin-resistant strains. As can be seen in Table 3, the rates of penicillin resistance, both intermediate and high-level resistance, varied from 16.1 to 24.0% throughout the 5-year study. It appears that in the first 3 years, from 1997 to 1999 inclusive, there was a decrease in the rate of penicillin resistance; however, from 1999 to 2002 inclusive, there was not only an increase in the rate of penicillin resistance but also an increase in the rate of high-level penicillin resistance from 2.4 to 13.8% ($P = 0.001$) (Table 3).

The rates of amoxicillin-clavulanate resistance (breakpoints for intermediate resistance and resistance, 4 and ≥8 μg/ml, respectively) were maintained at a low level, varying from 0 to 1% over the study period. The rates of resistance to cefuroxime, a representative expanded-spectrum cephalosporin, ranged from 8.3 to 10.5% (Table 3) and did not change over the 5-year study period. Table 4 shows that the impact of service, gender, and age group on the prevalence of penicillin-intermediate and penicillin-resistant *S. pneumoniae* isolates was minimal. As well, the impact of service, gender, and age group on resistance to cephalosporins such as cefuroxime was limited. Table 5 describes the MIC distributions of penicillin over the 5-year study period. As can be observed, there appears to have been a rightward shift (a shift to higher MICs) in the distribution of the penicillin MICs over the last 3 years of the study (1999 to 2002); however, no isolates for which penicillin MICs were >8 μg/ml were found. The distributions of the MICs of amoxicillin-clavulanate are described in Table 5. No rightward shift in amoxicillin-clavulante MICs occurred. For cefuroxime, the MIC distribution data showed that the

TABLE 2. In vitro activities of antibiotics against 6,991 *S. pneumoniae* isolates[a]

Antibiotic	All strains (*n* = 6,991)					Penicillin susceptible (*n* = 5,579 [79.8%])					Penicillin intermediate (*n* = 1,023 [14.6%])					Penicillin resistant (*n* = 389 [5.6%])				
	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)	MIC range (μg/ml)	% I	% R	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)	MIC range (μg/ml)	% I	% R	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)	MIC range (μg/ml)	% I	% R	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)	MIC range (μg/ml)	% I	% R
Penicillin	0.03	0.5	≤0.03–8	14.6	5.6	0.03	0.06	≤0.03–0.06	0	0	0.25	1.0	0.12–1	100	0	2	4	2–8	0	100
Amoxicillin-clavulanate[b]	0.03	0.25	≤0.03–8	0.8	0.1	0.03	0.03	≤0.03–0.5	0	0	0.12	1.0	0.03–4	1.9	0	1	4	0.12–8	9.2	1.1
Cefuroxime[c]	0.25	1.0	≤0.12–16	4.7	5.9	0.25	0.25	≤0.25–2	0.1	0	0.25	2	0.12–16	20.2	9.0	4	8	1–≥16	27.2	65.1
Cefprozil	0.25	1.0	≤0.25–16	3.4	3.9	0.25	0.25	≤0.25–2	0	0	0.5	4	0.25–16	7.5	5.9	4	8	1–≥16	31.8	42.3
Cefixime	0.25	4	≤0.06–16			0.25	0.25	≤0.06–4			1	8	0.12–>8			16	>16	4–>16		
Cefaclor	1	16	≤0.25–>16	7.2	12.0	1	1	≤0.25–16	5.7	0.5	2	16	1–>16	16.0	47.1	>16	>16	8–>16	2.8	95.3
Cefotaxime[c]	0.06	0.25	≤0.06–4	0.2	0.1	0.06	0.06	≤0.06–0.06	0	0	0.12	0.5	≤0.06–2	0.2	0	0.5	1	0.25–4	3.1	1.2
Ceftriaxone[c]	0.06	0.25	≤0.06–2	0.1	0	0.06	0.06	≤0.06–0.06	0	0	0.06	0.12	≤0.06–1	0	0	0.5	1	0.25–2	2.2	0
Imipenem	0.06	0.12	≤0.06–0.25	8.7	0	≤0.06	0.06	≤0.06–0.06	0	0	0.06	0.06	0.06–0.12	0	0	0.25	0.25	0.12–0.25	6.0	0
Meropenem	0.06	0.25	≤0.06–1	9.7	1.0	≤0.06	0.06	≤0.06–0.06	0	0	0.06	0.12	0.06–0.12	0	0	0.5	0.5	0.25–1	66.7	6.7
Erythromycin	0.25	0.5	≤0.25–>128	1.0	8.8	0.25	0.25	≤0.25–>128	0.5	4.4	0.25	4	0.25–>128	2.6	20.4	0.25	8	0.25–>128	4.1	45.1
Azithromycin	0.12	0.5	≤0.12–>128	1.6	8.1	0.12	0.12	≤0.12–>128	0.7	3.5	0.12	32	0.12–>128	3.5	23.3	0.12	32	0.12–>128	9.4	35.0
Clarithromycin	0.12	0.25	≤0.12–>128	2.0	7.6	0.12	0.12	≤0.12–>128	0.8	3.3	0.12	4	0.12–>128	5.2	21.4	0.12	8	0.12–>128	11.0	33.0
Clindamycin	0.12	0.12	≤0.12–8	0.5	3.3	0.12	0.12	≤0.12–8	0.3	1.2	0.12	4	0.12–8	1.1	11.9	0.12	1	0.12–8	1.6	10.5
Tetracycline	0.25	4	≤0.25–32	0.9	9.5	0.25	0.5	≤0.25–32	0.8	4.5	0.5	32	≤0.25–32	0.8	28.9	8	≥32	0.25–≥32	2.8	50.5
Doxycycline	0.25	0.5	≤0.25–32	3.1	2.4	0.25	0.25	≤0.25–32	0.7	0.4	0.25	8	≤0.25–32	10.9	11.1	0.25	4	0.25–16	17.1	9.2
Chloramphenicol	1	2	≤0.5–32	0	3.9	1	2	≤0.15–16	0	1.1	2	4	0.5–32	0	9.0	2	16	1–32	0	44.0
TMP/SMX	0.25	4	≤0.12–32	4.6	14.4	0.12	1	≤0.12–32	4.4	5.0	1	8	≤0.12–32	6.4	40.9	4	16	0.12–32	2.5	79.3
Vancomycin	0.25	0.5	≤0.25–1	0	0	0.25	0.5	≤0.25–1	0	0	0.25	0.5	≤0.25–1	0	0	0.25	0.5	≤0.25–1	0	0
Quinupristin-dalfopristin	0.25	0.5	≤0.12–2	0.1	0	0.25	0.5	≤0.12–2	0.1	0	0.25	0.5	≤0.12–2	0.1	0	0.25	0.5	≤0.12–1	0	0
Ciprofloxacin	1	2	0.12–64			1	2	0.12–64			1	2	0.12–64			1	2	0.25–64		
Levofloxacin	1	1	≤0.12–32	0.2	0.6	1	1	0.12–32	0.2	0.6	1	1	0.12–32	0.4	0.5	1	2	0.25–32	0	1.2
Gatifloxacin	0.25	0.5	≤0.06–16	0.3	0.6	0.25	0.5	0.06–16	0.2	0.6	0.25	0.5	0.06–16	0.5	0.5	0.25	0.5	0.12–16	0.5	0.5
Moxifloxacin	0.12	0.25	≤0.06–8	0.3	0.3	0.12	0.25	0.06–8	0.3	0.2	0.12	0.25	0.06–8	0.4	0.3	0.12	0.25	0.06–8	0.3	0.9
Trovafloxacin	0.12	0.12	≤0.06–8	0.3	0.3	0.12	0.12	0.06–8	0.3	0.2	0.12	0.25	0.06–8	0.4	0.3	0.12	0.25	0.06–8	0.3	0.9
Gemifloxacin	0.015	0.03	≤0.015–4			0.015	0.03	≤0.015–4			0.015	0.03	≤0.015–4			0.03	0.03	≤0.015–4		
Grepafloxacin	0.25	0.25	≤0.06–16	0.3	0.6	0.12	0.25	≤0.06–16	0.2	0.6	0.25	0.5	≤0.06–16	0.5	0.5	0.12	0.5	≤0.06–16	0.2	1.0
Clinafloxacin	0.06	0.06	≤0.06–1			0.06	0.06	≤0.06–1			≤0.06	0.12	≤0.06–1			0.06	0.06	≤0.06–1		
Linezolid	0.5	1	≤0.06–2	0	0	0.5	1	≤0.06–2	0	0	0.5	1	≤0.06–2	0	0	0.5	1	0.12–2	0	0
Telithromycin	0.008	0.015	≤0.002–8			0.008	0.008	0.002–8			0.008	0.03	0.002–0.5			0.008	0.06	0.002–1		
ABT-773	0.004	0.008	≤0.002–1			0.004	0.004	0.002–1			0.004	0.015	0.002–0.06			0.004	0.03	0.002–0.12		
ABT-492	0.008	0.015	≤0.008–0.5			0.008	0.015	≤0.008–0.5			0.008	0.015	≤0.008–0.5			0.015	0.015	≤0.008–0.5		
Ertapenem	0.015	0.25	≤0.015–2			0.015	0.03	≤0.015–0.5			0.06	0.5	0.015–1			0.5	0.5	≤0.015–2		
BMS284756 (garenoxacin)	0.06	0.06	≤0.015–4			0.06	0.06	≤0.015–4			0.06	0.06	≤0.015–4			0.06	0.12	≤0.015–4		
GAR-936 (tigecycline)	0.03	0.06	≤0.015–0.25			0.03	0.03	≤0.015–0.12			0.03	0.06	≤0.015–0.12			0.03	0.06	≤0.015–0.25		

[a] % I, percentage of isolates with intermediate resistance; % R, percentage of resistant isolates.
[b] The percentages of intermediate and resistant isolates are based on NCCLS breakpoints of 4 and ≥8 μg/ml, respectively.
[c] The percentages of intermediate and resistant isolates are based on NCCLS breakpoints of 2 and ≥4 μg/ml, respectively.

TABLE 3. Antibiotic resistance among *S. pneumoniae* isolates from 1997 to 2002

Yr	No. of isolates	% Antibiotic resistance[a]							
		Penicillin	Amox/Clav	Cefuroxime	Clarithromycin	Doxycycline	TMP-SMX	Levofloxacin	Multiple drugs
1997–1998	1,180	21.2 (14.8, 6.4)	1.0 (0.8, 0.2)	10.5 (4.5, 6.0)	7.9 (2.2, 5.7)	3.2 (2.0, 1.2)	21.8 (8.1, 13.7)	0.5 (0.3, 0.2)	2.7
1998–1999	1,333	19.6 (17.3, 2.3)	1.0 (0.8, 0.2)	9.0 (4.7, 4.3)	9.8 (2.1, 7.8)	4.9 (3.2, 1.7)	22.0 (7.7, 14.3)	0.7 (0.2, 0.5)	4.7
1999–2000	1,593	16.1 (13.7, 2.4)	0.3 (0.2, 0.1)	8.3 (4.2, 4.1)	9.0 (1.7, 7.3)	5.1 (3.4, 1.7)	19.8 (6.7, 13.1)	1.1 (0.1, 1.0)	6.4
2000–2001	1,435	22.1 (13.2, 8.9)	0.3 (0.1, 0.1)	10.2 (4.3, 5.9)	9.1 (1.5, 7.6)	6.6 (3.1, 3.5)	25.8 (9.6, 16.2)	0.8 (0.1, 0.7)	8.1
2001–2002	1,450	24.0 (10.2, 13.8)	0	9.3 (4.4, 4.9)	11.1 (2.3, 8.8)	3.1 (1.9, 1.2)	24.0 (7.6, 16.4)	1.1 (0.2, 0.9)	8.8

[a] Intermediate plus high-level resistance; values in parentheses are intermediate and high-level resistance rates, respectively.

MICs were ≤0.25 μg/ml for the majority of isolates, with a few strains with high-level resistance (MICs, 16 and ≥32 μg/ml) being reported. No rightward shift in the cefuroxime MIC distribution was observed.

Three macrolides were examined over the 5 years of the study, including erythromycin, clarithromycin, and azithromycin. Even though the NCCLS breakpoints differ (29) for each macrolide, when the percentages of intermediate and fully resistant isolates are added, the rates of resistance to all macrolides were similar (approximately 10%) (Table 2). The rates of resistance to macrolides were the lowest among the penicillin-susceptible strains (approximately 4 to 5%), but this increased to 20 to 25% among the penicillin-intermediate strains and to approximately 40 to 50% among the penicillin-resistant strains (Table 2). As described in Table 3, in Canada the rates of resistance (intermediate and resistant) to clarithromycin, a representative macrolide, increased from 7.9 to 11.1% over the 5-year study period. The rates of resistance to macrolides were not influenced by service, gender, or age group (Table 4). When the distributions of the MICs of the macrolides are analyzed, it is clear that the MICs were ≤0.03 μg/ml for the majority of strains. However, greater than 60% of macrolide-resistant strains (clarithromycin MICs, ≥1 μg/ml) appeared to demonstrate a macrolide resistance phenotype (M phenotype; macrolide MICs of 1 to 16 μg/ml and susceptibility to clindamycin), whereas approximately 40% of strains demonstrated a macrolide, lincosamide, and streptogramin B resistance phenotype (MLS_B phenotype; macrolide MICs of ≥32 μg/ml and resistance to clindamycin). It should be stated that, on the basis of the MIC distributions, the incidences of the M and MLS_B phenotypes did not change over the 5-year study period (Table 5).

The rates of resistance (intermediate and resistant) to other antimicrobials were as follows: clindamycin, 3.8%; doxycycline, 5.5%; chloramphenicol, 3.9%; TMP-SMX, 19.0%; vancomycin, 0%; quinupristin-dalfopristin, 0.1%; and linezolid, 0%. The rates of resistance to β-lactam agents (penicillins and cephalosporins), as well as carbapenems, macrolides, clindamycin, tetracyclines such as doxycycline, chloramphenicol, and TMP-SMX increased as the penicillin resistance changed from penicillin intermediate to penicillin resistant (Table 2). No resistance to vancomycin and linezolid was noted among the penicillin-resistant strains. Among the fluoroquinolones, the order of activity based on the MIC_{50}s and MIC_{90}s was gemifloxacin > clinafloxacin > trovafloxacin > moxifloxacin > grepafloxacin > gatifloxacin > levofloxacin > ciprofloxacin. The rates of resistance to the fluoroquinolones were the highest among the penicillin-resistant strains (Table 2). As described in Table 3, the rate of resistance to fluoroquinolones, with levofloxacin used as a representative fluoroquinolone, varied from 0.5 to 1.1%. The rate of resistance to levofloxacin was higher for isolates from inpatients, those from females, and those from patients ≥65 years of age (Table 4). The distribution of the levofloxacin MICs suggested that the MICs were 0.5 and 1.0 μg/ml for the majority of isolates, and no rightward shift in the MIC distribution occurred over the 5-year study period. The investigational fluoroquinolones BMS284756 (garenoxacin) and ABT-492 both demonstrated excellent activities against the *S. pneumoniae* isolates, with MIC_{90}s of 0.06 and 0.015 μg/ml, respectively (Table 2). Two

TABLE 4. Rates of recovery of *S. pneumoniae* isolates with intermediate and high levels of antibiotic resistance by service, gender, and age[a]

Characteristic	Total no. (%) of isolates	Penicillin		Cefuroxime		Clarithromycin		Doxycycline		Levofloxacin	
		% I	% R	% I	% R	% I	% R	% I	% R	% I	% R
Service											
Inpatient	3,770 (53.9)	15.1	6.4	4.9	5.9	2.0	7.6	3.2	2.7	0.1	0.8
Outpatient	3,221 (46.1)	14.1	4.6	4.5	5.8	2.1	7.5	3.1	2.2	0.2	0.4
Gender											
Female	2,762 (39.5)	12.8	5.2	4.7	5.9	2.1	7.6	2.9	2.7	0.1	0.9
Male	4,229 (60.5)	15.8	5.8	4.7	5.8	2.0	7.5	3.3	2.3	0.2	0.4
Age group											
≤16 yr	1,522 (21.8)	16.7	5.9	4.6	5.9	1.8	7.8	4.0	2.2	0.0	0.0
17–64 yr	2,782 (39.8)	14.0	5.3	4.8	5.7	3.2	7.6	2.5	2.7	0.3	0.4
≥65 yr	2,687 (38.4)	14.2	5.9	4.7	5.8	1.8	7.4	3.3	2.4	0.1	1.1

% I, percentage of isolates with intermediate resistance; % R, percentage of resistant isolates.

TABLE 5. Distribution of MICs of selected antibiotics for the *S. pneumoniae* isolates tested

Antibiotic and yr	No. of isolates	% of isolates for which MICs (μg/ml) were:															
		≤0.03	0.06	≤0.12	0.12	≤0.25	0.25	0.5	1	2	4	8	16	≥16	32	≥32	64	≥128
Penicillin																		
1997–1998	1,180	54.6	24.2		5.5		2.3	2.8	4.2	3.6	2.1	0.7						
1998–1999	1,333	58.0	22.2		5.7		2.0	3.1	6.5	1.9	0.4							
1999–2000	1,593	65.1	18.7		3.9		2.1	2.6	5.1	2.3	0.1							
2000–2001	1,435	47.3	29.8		5.2		3.8	2.1	2.1	4.3	4.5	0.1						
2001–2002	1,450	44.4	31.4		3.4		3.8	1.9	1.1	8.4	5.4							
Amoxicillin-clavulanate																		
1997–1998	1,180	80.7	3.2		3.5		2.4	3.2	3.5	2.6	0.8	0.2						
1998–1999	1,333	80.9	3.4		3.5		2.2	3.0	3.5	2.6	0.8	0.2						
1999–2000	1,593	83.6	2.9		2.8		1.9	2.7	3.9	1.9	0.2	0.1						
2000–2001	1,435	82.9	3.2		2.6		2.8	3.6	4.0	0.8	0.1	0.1						
2001–2002	1,450	77.7	2.9		2.9		1.9	3.9	8.7	3.3								
Cefuroxime																		
1997–1998	1,180					85.3		2.4	1.8	4.5	5.2	0.7	0.1					
1998–1999	1,333					87.3		1.5	2.2	4.7	4.1	0.1	0.1					
1999–2000	1,593					87.9		2.3	1.5	4.2	3.5	0.3	0.3					
2000–2001	1,435					86.3		1.7	2.0	4.3	4.5	1.2	0.1			0.1		
2001–2002	1,450					90.2		1.5	1.4	4.4	3.4	1.4	0.1					
Clarithromycin																		
1997–1998	1,180	80.5	8.5		1.7		1.3	2.2	1.6	0.3	1.0	0	0.4		0.1		0.2	2.1
1998–1999	1,333	79.5	7.8		0.6		2.3	2.1	3.1	1.4	0.9	0.2	0.4		0.1		0.1	1.5
1999–2000	1,593	79.0	8.7		2.4		1.0	1.7	1.7	1.4	1.3	0.3	0.2		0.1		0.2	2.1
2000–2001	1,435	85.3	1.9		1.9		1.9	1.5	1.9	1.5	0.4	1.1	0		0.8		0	1.9
2001–2002	1,450	86.6	1.1		0.4		0.8	2.3	1.9	2.3	1.5	0.4	0.4		0		0.4	1.9
Doxycycline																		
1997–1998	1,180					91.8		2.4	1.2	1.4	2.0	0.4	0.5			0.3		
1998–1999	1,333					89.0		2.2	1.0	2.2	3.2	0.9	0.7			0.1		
1999–2000	1,593					89.8		1.8	0.8	2.4	3.4	0.9	0.7			0.1		
2000–2001	1,435					88.0		1.0	1.6	2.7	3.1	1.3	1.8			0.4		
2001–2002	1,450					92.0		2.3	1.1	1.5	1.9	0.4	0.4			0.4		
TMP-SMX																		
1997–1998	1,180			60.8			11.5	5.7	4.3	3.8	9.8	3.1		0.8				
1998–1999	1,333			53.3			19.1	5.7	3.7	4.0	10.0	3.8		0.5				
1999–2000	1,593		52.4			22.2	5.8	4.5	2.2	8.7	4.1		0.3					
2000–2001	1,435		38.4			20.8	14.8	5.7	3.9	5.8	4.6		5.8					
2001–2002	1,450		21.5			24.1	30.3	4.2	3.4	1.1	8.4		6.9					
Levofloxacin																		
1997–1998	1,180		1.6		2.4		26.8	64.0	4.7	0.3	0.1	0.1						
1998–1999	1,333		1.5		5.3		22.0	67.1	3.5	0.2	0.3	0.2						
1999–2000	1,593		1.3		2.2		12.9	77.2	5.3	0.1	0.4	0.2			0.4			
2000–2001	1,435		1.5		6.5		33.4	53.8	5.1	0.1	0.1	0.6						
2001–2002	1,450		1.0		0.5		28.2	63.8	4.2	0.2	0.6	0.2			0.1			

investigational ketolides, telithromycin and ABT-773, were studied. The MIC_{90}s of telithromycin and ABT-773 were 0.015 and 0.008 μg/ml, respectively. The MIC_{90}s of both ketolides increased for penicillin-intermediate and penicillin-resistant *S. pneumoniae* isolates relative to those for penicillin-susceptible strains. An investigational glycylcycline, GAR-936 (tigecycline), demonstrated excellent activities against penicillin-susceptible as well as penicillin-resistant *S. pneumoniae* isolates, with MIC_{90}s of 0.06 μg/ml (Table 2).

Table 3 describes the incidence of a multidrug resistance phenotype over the 5-year study period. The multidrug resistance phenotype was defined as resistance to three or more classes of antimicrobials, including β-lactams, macrolides, tetracyclines, TMP-SMX, and fluoroquinolones. The proportions of isolates with the multidrug resistance phenotype increased in every year of the study, from 2.7% in 1997-1998 to 8.8% in 2001-2002 ($P < 0.001$) (Table 3).

Table 6 compares the rates of resistance to penicillin, macrolides (clarithromycin), and fluoroquinolones (levofloxacin) by province or region of Canada. The major observation was that considerable variation occurred both within and between each province or region in a given year. However, general trends were observed. Consistently, the highest rates of penicillin nonsusceptibility were observed in western Canada (e.g., Saskatchewan), while the lowest rates of penicillin resistance occurred in the Maritime provinces (Table 6). Macrolide re-

TABLE 6. Rates of resistance to selected antimicrobials by province or region, 1997 to 2002[a]

Province region (range of no. of isolates/yr)	Rate (%) of resistance[a]																							
	1997–1998					1998–1999					1999–2000					2000–2001					2001–2002			
	Pen^s	I	R	Mac^r	FQ^r	Pen^s	I	R	Mac^r	FQR	Pen^s	I	R	Mac^r	FQ^r	Pen^s	I	R	Mac^r	FQ^r	Pen^s	I	R	Mac^r
British Columbia (144–158)	77.6	14.9	7.5	12.9	0	78.1	21.2	0.7	10.2	0.7	89.6	9.0	1.4	9.0	1.4	80.6	12.0	1.4		0	81.1	9.9	9.9	7.2
Alberta (149–196)	75.0	18.7	6.3	9.4	0.5	81.2	16.8	2.0	10.7	0.5	81.9	15.4	2.7	11.4	2.0	73.3	17.0	9.7	8.0	0	75.5	12.1	13.5	9.7
Saskatchewan (130–187)	65.4	22.3	12.3	10.8	0	60.2	29.5	10.3	12.3	0.7	75.9	20.3	3.7	9.1	1.1	65.3	23.6	11.1	13.9	1.4	65.2	21.1	13.9	12.4
Manitoba (122–173)	72.6	17.7	9.7	1.6	1.6	79.3	20.0	0.7	3.6	0.7	79.8	19.7	0.6	5.2	1.2	80.3	9.8	9.8	9.9	0.8	79.5	9.9	13.4	8.9
Ontario (98–439)	77.6	9.2	13.2	9.2	6.1	85.7	12.3	2.0	5.9	1.5	84.3	13.2	2.5	9.6	0.7	82.2	12.6	5.1	8.7	1.6	81.1	10.5	8.8	9.9
Quebec (233–327)	75.5	19.7	4.8	9.0	0.4	82.0	16.4	1.6	15.2	0.3	80.0	14.5	5.5	13.1	1.5	74.3	14.2	11.5	13.2	0.4	73.3	10.1	14.2	14.2
Maritimes (181–256)	95.3	3.9	0.8	4.9	3.5	90.0	9.4	0.6	7.7	0	90.7	8.4	0.9	7.1	0.9	80.2	14.0	5.8	8.3	0.8	78.8	10.0	7.8	12.1
Total for Canada	78.8	14.8	6.4	7.9	0.5	80.4	17.3	2.3	9.8	0.7	83.9	13.7	2.4	9.0	1.1	79.9	13.2	8.9	9.1	0.8	76.0	10.2	13.8	11.1

[a] Pen^s, penicillin-susceptible (MIC ≤0.06 μg/ml); I, penicillin intermediate (MIC 0.12 to 1 μg/ml); R, penicillin resistant (MIC, ≥2 μg/ml); Mac^r macrolide (clarithromycin) intermediate and resistant (MICs, ≥0.5 μg/nl); FQ^r, fluoroquinolone (levofloxacin) intermediate and resistant (MICs, ≥4 μg/ml).

sistance tended to be lowest in British Columbia and Manitoba and highest in Quebec. The rate of fluoroquinolone resistance was observed to be low (~1%) in all parts of the country.

DISCUSSION

CROSS is an ongoing longitudinal surveillance program that studies the incidence of antibiotic resistance in respiratory pathogens across all regions of Canada (37). Thus, it represents a unique opportunity to compare rates of antibiotic resistance among isolates from various geographically distributed medical centers, among isolates from patients with different demographic profiles, and by antimicrobial class. From 1997 to 2002, the same 25 medical centers participated in the study during all 5 years of the study. Each year large numbers (1,180 to 1,593) of respiratory tract *S. pneumoniae* isolates were isolated and collected during the same time of year (during the winter months). Over the 5-year study period, the study demographics remained constant, in that the specimen type was primarily sputum specimens, bronchoalveolar lavage specimens, and endotracheal secretions. The breakdown of the isolates by service was approximately 54% inpatient and 46% outpatient. The breakdown of the isolates by gender was approximately 40% female and 60% male, and the breakdown of the isolates by age was approximately 20% from those ≤16 years of age, 40% from those 17 to 64 years of age, and 40% from those >65 years of age (Tables 1 and 4).

This study found that the rate of penicillin resistance (intermediate and resistant) did not significantly change over the 5-year period and ranged from 21.2% in 1997-1998 to 24.0% in 2001-2002. However, in the last 3 years of the study a dramatic increase in the proportion of isolates with high-level penicillin resistance (MICs, ≥2 μg/ml), which increased from 2.4% in 1999-2000 to 13.8% in 2001-2002, occurred ($P = 0.001$) (Table 3). The same observation has been made previously (11, 36). For the majority of these highly penicillin resistant isolates, the penicillin MICs were 2 to 4 μg/ml; however, for some strains the penicillin MICs were 8 μg/ml (Table 5). This is particularly worrisome, as high-level penicillin-resistant strains may be more likely to be associated not only with cross-resistance to other antimicrobial classes but also with failure with β-lactams (2, 24).

As would be expected, when the isolates were grouped by penicillin susceptibility categories, the rates of resistance to all β-lactams, including penicillins, cephalosporins, and carbapenems, increased in parallel with increasing penicillin resistance. This is not surprising, as penicillin resistance in *S. pneumoniae* is the result of alterations in penicillin binding proteins, and all β-lactam and β-lactam like agents bind at least to some extent to the same penicillin binding proteins (3, 7, 9, 12, 15).

Rates of resistance (intermediate and resistant) to non-β-lactam agents were approximately 3.8% for clindamycin, 5.5% for doxycycline, 3.9% for chloramphenicol, and 19.0% for TMP-SMX; and these rates did not change over the 5-year study period (Tables 2 and 3). The rates of resistance to all non-β-lactam antibiotics were consistently higher among the penicillin-intermediate and penicillin-resistant *S. pneumoniae* isolates than among their penicillin-susceptible counterparts. Vancomycin and linezolid consistently showed excellent activities, and no resistance was observed. Macrolide resistance, as depicted for clarithromycin, a representative macrolide, increased significantly over the 5-year study period, from 7.9% in 1997-1998 to 11.1% in 2001-2002 (Table 3). The phenotypic expression of macrolide resistance was consistent with both efflux-based (M phenotype) and target-based (MSL_B phenotype) resistance (11, 38, 39). We previously reported that the M phenotype predominates over the MLS_B phenotype, as determined by PCR (18). Other North American studies have also concluded that the M phenotype predominates (11, 17, 33, 34, 36, 37). Unlike other investigators (13, 19), we have not observed a rightward shift in the MIC distribution, with higher MICs for isolates with the efflux-based phenotype observed over time. The investigational ketolides telithromycin and ABT-773 (38) demonstrated excellent activities against penicillin-susceptible and penicillin-nonsusceptible *S. pneumoniae* isolates, with MIC_{90}s of 0.015 and 0.008 μg/ml, respectively

(Table 2). It should be noted, however, that the ketolide MICs were elevated for some penicillin-nonsusceptible isolates. The investigational glycylcycline GAR-936 (tigecycline) demonstrated excellent activities against penicillin-susceptible as well as penicillin-nonsusceptible *S. pneumoniae* isolates, with MIC_{90}s of 0.06 μg/ml (Table 2).

The activities of fluoroquinolones, as measured by the MIC_{90}s (which are given in parentheses), were gemifloxacin (0.03 μg/ml) > clinafloxacin (0.06 μg/ml) > trovafloxacin (0.12 μg/ml) > grepafloxacin (0.25 μg/ml) = moxifloxacin (0.25 μg/ml) > gatifloxacin (0.5 μg/ml) > levofloxacin (1 μg/ml) > ciprofloxacin (2 μg/ml) (Table 2). This order of fluoroquinolone activity has been reported previously (40). The investigational fluoroquinolones ABT-492 and BMS284756 (garenoxacin) also demonstrated excellent activities against *S. pneumoniae*, with MIC_{90}s of 0.015 and 0.06 μg/ml, respectively (Table 2). As displayed in Table 3, the rates of resistance (intermediate and resistant) to fluoroquinolones, as depicted by levofloxacin, continues to range from 0.5 to 1.1% among isolates in Canada. Thus, following the observation of Chen et al. (8) of increasing ciprofloxacin resistance in Canada and globally (4, 16, 22, 26, 31, 40), the use of new fluoroquinolones such as gatifloxacin, levofloxacin, and moxifloxacin has not led to date to a rapid escalation in the rates of resistance to the new fluoroquinolone agents in Canada. We have not observed a rightward shift in the distributions of the MICs of the new fluoroquinolones such as levofloxacin (Table 5); however, these MIC frequency distributions need to be continuously monitored over time, especially among isolates from inpatients and elderly individuals, to alert clinicians and researchers to any increasing shift in fluoroquinolone MICs. For levofloxacin-resistant isolates (MICs, ≥8 μg/ml), the corresponding ciprofloxacin MICs were 16 to 64 μg/ml, the gatifloxacin MICs were 2 to 16 μg/ml, the moxifloxacin MICs were 1 to 16 μg/ml, the gemifloxacin MICs were 0.12 to 4 μg/ml, the ABT-492 MICs were 0.06 to 0.5 μg/ml, and the BMS284756 (garenoxacin) MICs were 0.25 to 8 μg/ml (data not shown). It should be mentioned that isolates with high-level fluoroquinolone resistance, as depicted by levofloxacin MICs of ≥8 μg/ml, were frequently resistant to penicillin as well as non-β-lactam agents.

We have demonstrated in this multiyear surveillance study that although the proportions of penicillin-resistant (intermediate and resistant) *S. pneumoniae* isolates remained relatively stable, the rate of high-level penicillin resistance increased, as did the rate of multidrug resistance (Table 3). In fact, the proportions of *S. pneumoniae* isolates with the multidrug resistance phenotype increased from 2.7% in 1997-1998 to 8.8% in 2001-2002 ($P < 0.001$). The increase in the proportions of *S. pneumoniae* isolates with the multidrug-resistant phenotype has previously been shown by Doern et al. (11) as well as Whitney et al. (36). One potential explanation for the increase in high-level penicillin resistance and multidrug resistance is the continuous proliferation of a few "fit" clones that are high-level penicillin resistant and/or multidrug resistant. This has been reported in the United States and continues to evolve (9, 11). Doern et al. (11) have suggested that 9 to 10 major clones of penicillin-resistant *S. pneumoniae* isolates exist in the United States and comprise 70 to 80% of penicillin-resistant *S. pneumoniae* isolates. We believe that these same fit clones exist in Canada and appear to be proliferating (data not shown). We hypothesize that the rapid dissemination of high-level penicillin-resistant and multidrug-resistant *S. pneumoniae* isolates in Canada is continuing due to the rapid proliferation of these fit clones.

The influence of patient demographics on *S. pneumoniae* has been shown in Table 4. In brief, we observed that inpatient or outpatient service had little impact on resistance, nor did gender. However, we did observe a higher incidence of fluoroquinolone resistance among isolates from inpatients and subjects ages ≥65 years. It remains essential to monitor the evolution of fluoroquinolone resistance in this patient population.

In conclusion, the rate of antimicrobial resistance among *S. pneumoniae* isolates in Canada continues to grow. Over the last 3 years we have observed the rapid evolution of highly penicillin-resistant as well as multidrug-resistant *S. pneumoniae* isolates. As well, the rate of macrolide resistance continues to grow, but the rate of resistance to the new fluoroquinolones appears to be stable at approximately 0.5 to 1%.

ACKNOWLEDGMENTS

CROSS surveillance sites and investigators were as follows: Victoria General Hospital, Victoria, British Columbia, P. Kibsey; Vancouver Hospital, Vancouver, British Columbia, D. L. Roscoe; Calgary Lab Services, Calgary, Alberta, D. Church; University of Alberta Hospitals, Edmonton, Alberta, R. P. Rennie; Regina General Hospital, Regina, Saskatchewan, E. Thomas; Royal University Hospital, Saskatoon, Saskatchewan, J. M. Blondeau; St. Boniface Hospital, Winnipeg, Manitoba, G. K. M. Harding; Health Sciences Centre, Winnipeg, Manitoba, D. J. Hoban and G. G. Zhanel; St. Joseph's Hospital, Hamilton, Ontario, D. Groves; Hamilton Health Sciences Centre, Hamilton, Ontario, F. Smaill; McMaster, Hamilton, Ontario, M. Loeb; Mount Sinai Hospital, Toronto, Ontario, D. Low; London Health Sciences Centre, London, Ontario, Z. Hussain; Ottawa General Hospital, Ottawa, Ontario, K. Ramotar; Children's Hospital of Eastern Ontario, Ottawa, Ontario, F. Chan; Montreal Children's Hospital, Montreal, Quebec, J. McDonald; Montreal Jewish General Hospital, Montreal, Quebec, A. Dascal; Maisonneuve-Rosemont, Montreal, Quebec, M. Laverdiere; Montreal General Hospital, Montreal, Quebec, V. Loo; Hotel-Dieu of Montreal, Montreal, Quebec, M. Poisson; Universitaire de Sante de l'Estrie, Sherbrooke, Quebec, J. Dubois; South East Health Care Corp., Moncton, New Brunswick, M. Kuhn; St. John Regional, St. John, New Brunswick, G. Hardy and Y. Yaschuk; Queen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia, K. Forward and R. Davidson; and Queen Elizabeth Hospital, Charlottetown, Price Edward Island, L. Abbott.

We thank M. Wegrzyn for expert secretarial assistance. Funding for the CROSS study was provided in part by Abbott Laboratories Ltd., Astra Zeneca, Aventis Pharma, Bayer Inc., Bristol-Myers Squibb Pharmaceutical Group, GlaxoSmithKline, Janssen-Ortho Inc., Merck Frosst Canada & Co., Pharmacia Upjohn, Pfizer, and Wyeth.

REFERENCES

1. **Appelbaum, P. C.** 1997. Antimicrobial resistance in *Streptococcus pneumoniae*: an overview. Clin. Infect. Dis. **15:**77–83.
2. **Ball, P.** 1999. Therapy for pneumococcal infection at the millennium: doubts and certainties. Am. J. Med. **107**(Suppl. 1A)**:**77S–85S.
3. **Barcus, V. A., K. Ghanekar, M. Yeo, T. J. Coffey, and C. G. Dowson.** 1995. Genetics of high-level penicillin resistance in clinical isolates of *Streptococcus pneumoniae*. FEMS Microbiol. Lett. **126:**299–304.
4. **Barry, A. L., S. D. Brown, and P. C. Fuchs.** 1999. Fluoroquinolone resistance among recent clinical isolates of *Streptococcus pneumoniae*. J. Antimicrob. Chemother. **43:**428–429.
5. **Bartlett, J. G., R. F. Breiman, L. A. Mandell, and T. M. File, Jr.** 1998. Community-acquired pneumonia in adults: guidelines for management. Clin. Infect. Dis. **26:**811–838.
6. **Butler, J. C., J. Hofmann, M. S. Cetron, J. A. Elliott, R. R. Facklam, and R. F. Breiman.** 1996. The continued emergence of drug-resistant *Streptococcus pneumoniae* in the United States: an update from the Centers for Disease

Control and Prevention's Pneumococcal Sentinel Surveillance System. J. Infect. Dis. **174:**986–993.
7. **Chalkley, L. J., and H. J. Koornhof.** 1990. Intra- and interspecific transformation of *Streptococcus pneumoniae* to penicillin resistance. J. Antimicrob. Chemother. **26:**21–28.
8. **Chen, D. K., A. McGeer, J. C. de Azavedo, and D. E. Low.** 1999. Decreased susceptibility of *Streptococcus pneumoniae* to fluoroquinolones in Canada. N. Engl. J. Med. **341:**233–239.
9. **Coffey, T. J., M. Daniels, L. K. McDougal, C. G. Dowson, F. C. Tenover, and B. G. Spratt.** 1995. Genetic analysis of clinical isolates of *Streptococcus pneumoniae* with high-level resistance to expanded-spectrum cephalosporins. Antimicrob. Agents Chemother. **39:**1306–1313.
10. **Del Beccaro, M. A., P. M. Mendelman, A. F. Inglis, M. A. Richardson, N. O. Duncan, C. R. Clausen, and T. L. Stull.** 1992. Bacteriology of acute otitis media: a new perspective. J. Pediatr. **120:**81–84.
11. **Doern, G. V., K. P. Heilmann, H. K. Huynh, P. R. Rhomberg, S. L. Coffam, and A. B. Brueggemann.** 2001. Antimicrobial resistance among clinical isolates of *Streptoccoccus pneumoniae* in the United States during 1999–2000 including a comparison of rates since 1994–1995. Antimicrob. Agents Chemother. **45:**1721–1729.
12. **Dowson, C. G., A. Hutchinson, J. A. Brannigan, R. C. George, D. Hansman, J. Liñares, A. Tomasz, J. M. Smith, and B. G. Spratt.** 1989. Horizontal transfer of penicillin-binding protein genes in penicillin-resistant clinical isolates of *Streptococcus pneumoniae*. Proc. Natl. Acad. Sci. USA **86:**8842–8846.
13. **Gay, K., W. Baughman, Y. Miller, D. Jackson, C. G. Whitney, A. Schuchat, M. M. Farley, F. Tenover, and D. S. Stephens.** 2000. The emergence of *Streptococcus pneumoniae* resistant to macrolide antimicrobial agents: a 6-year population-based assessment. J. Infect. Dis. **182:**1417–1424.
14. **Giesecke, J., and H. Fredlund.** 1997. Increase in pneumococcal bactaeremia in Sweden. Lancet **349:**699–700.
15. **Hakenbeck, R., M. Tarpay, and A. Tomasz.** 1980. Multiple changes of penicillin-binding proteins in penicillin-resistant clinical isolates of *Streptococcus pneumoniae.* Antimicrob. Agents Chemother. **17:**364–371.
16. **Ho, P. L., T. L. Que, D. N. Tsang, T. K. Ng, K. H. Chow, and W. H. Seto.** 1999. Emergence of fluoroquinolone resistance among multiply resistant strains of *Streptococcus pneumoniae* in Hong Kong. Antimicrob. Agents Chemother. **43:**1310–1313.
17. **Hoban, D. J., G. V. Doern, A. C. Fluit, M. Roussel-Delvallez, and R. N. Jones.** 2001. Worldwide prevalence of antimicrobial resistance in *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* in the Sentry antimicrobial surveillance program 1997–9. Clin. Infect. Dis. **32**(Suppl. 2)**:** 81–93.
18. **Hoban, D. J., A. Wierzbowski, A. K. Nichol, and G. G. Zhanel.** 2001. Macrolide-resistant *Streptococcus pneumoniae* in Canada from 1998 to 1999: prevalence of *mefA* and *ermB* and susceptibility to ketolides. Antimicrob. Agents Chemother. **45:**2147–2150.
19. **Hyde, T. B., K. Gay, D. S. Stephens, D. J. Vugia, M. Pass, S. Johnson, N. L. Barrett, W. Schaffner, P. R. Cieslak, P. S. Maupin, E. R. Zell, J. H. Jorgensen, R. R. Facklam, and C. G. Whitney.** 2001. Macrolide resistance among invasive *Streptococcus pneumoniae* isolates. JAMA **286:**1857–1862.
20. **Ip, M., D. J. Lyon, R. W. H. Yung, C. Chan, and A. F. B. Cheng.** 1999. Evidence of clonal dissemination of multidrug-resistant *Streptococcus pneumoniae* in Hong Kong. J. Clin. Microbiol. **37:**2834–2839.
21. **Jacobs, M. R., H. J. Koornhof, R. M. Robins-Browne, C. M. Stevenson, Z. A. Vermaak, I. Freiman, G. B. Miller, M. A. Witcomb, M. Isaacson, J. I. Ward, and R. Austrian.** 1978. Emergence of multiply resistant pneumococci. N. Engl. J. Med. **299:**735–740.
22. **Jones, M. E., D. F. Sahm, N. Martin, S. Scheuring, P. Heisig, C. Thornsberry, K. Kohrer, and F. J. Schmitz.** 2000. Prevalence of *gyrA*, *gyrB*, *parC*, and *parE* mutations in clinical isolates of *Streptococcus pneumoniae* with decreased susceptibilities to different fluoroquinolones and originating from worldwide surveillance studies during the 1997–1998 respiratory season. Antimicrob. Agents Chemother. **44:**462–466.
23. **Lovgren, M., J. S. Spika, and J. A. Talbot.** 1998. Invasive *Streptococcus pneumoniae* infections: serotype distribution and antimicrobial resistance in Canada, 1992–1995. Can. Med. Assoc. J. **158:**327–331.
24. **Low, D. E.** 1998. Resistance and treatment implications: *Pneumococcus*, *Staphylococcus aureus* and gram-negative rods. Infect. Dis. Clin. N. Am. **3:** 613–630.
25. **Mandell, L. A., T. J. Marrie, R. F. Grossman, A. W. Chow, R.H. Hyland, the Canadian Community Acquired Pneumonia Working Group.** 2000. Canadian guidelines for the initial management of community acquired pneumonia: an evidence based update of the Canadian Infectious Diseases Society and the Canadian Thoracic Society. Clin. Infect. Dis. **31:**383–421.
26. **McGee, L., C. E. Goldsmith, and K. P. Klugman.** 2002. Fluoroquinolone resistance among clinical isolates of Streptococcus pneumoniae belonging to international multiresistant clones. J. Antimicrob. Chemother. **49:**173–176.
27. **Musher, D. M.** 1992. Infections caused by *Streptococcus pneumoniae*: clinical spectrum, pathogenesis, immunity, and treatment. Clin. Infect. Dis. **14:**801–809.
28. **National Committee for Clinical Laboratory Standards.** 2000. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. Approved standard M7-A5, 5th ed. National Committee for Clinical Laboratory Standards, Wayne, Pa.
29. **National Committee for Clinical Laboratory Standards.** 2002. Performance standards for antimicrobial susceptibility testing: supplemental tables. M100-S12. National Committee for Clinical Laboratory Standards, Wayne, Pa.
30. **Pallares, R., J. Linares, M. Vadillo, C. Cabellos, F. Manresa, P. F. Viladrich, R. Martin, and F. Gudiol.** 1995. Resistance to penicillin and cephalosporin and mortality from severe pneumococcal pneumoniae in Barcelona, Spain. N. Engl. J. Med. **333:**474–480.
31. **Pan, X. S., J. Ambler, S. Mehtar, and L. M. Fisher.** 1996. Involvement of topoisomerase IV and DNA gyrase as ciprofloxacin targets in *Streptococcus pneumoniae*. Antimicrob. Agents Chemother. **40:**2321–2326.
32. **Plouffe, J. F., R. F. Breiman, R. R. Facklam, and the Franklin County Pneumonia Study Group.** 1996. Bacteremia with *Streptococcus pneumoniae*: implications for therapy and prevention. JAMA **275:**194–198.
33. **Simor, A. E., M. Louie, and D. E. Low for the Canadian Bacterial Surveillance Network.** 1996. Canadian national survey of prevalence of antimicrobial resistance among clinical isolates of *Streptococcus pneumoniae*. Antimicrob. Agents Chemother. **40:**2190–2193.
34. **Thornsberry, C., P. T. Ogilvie, H. P. Holley, and D. F. Sahm.** 1999. Survey of susceptibilities of *Streptococcus pneumoniae, Haemophilus influenzae*, and *Moxarella catarrhalis* isolates to 26 antimicrobial agents: a prospective U.S. study. Antimicrob. Agents Chemother. **43:**2616–2623.
35. **Tomasz, A.** 1999. New faces of an old pathogen: emergence and spread of multidrug-resistant *Streptococcus pneumoniae*. Am. J. Med. **107:**55S–62S.
36. **Whitney, C. G., M. M. Farley, and J. Hadler.** 2000. Increasing prevalence of multi-drug resistant *Streptococcus pneumoniae* in the United States. N. Engl. J. Med. **343:**1817–1824.
37. **Zhanel, G. G., J. A. Karlowsky, L. Palatnick, L. Vercaigne, D. E. Low, the Canadian Respiratory Infection Study Group, and D. J. Hoban.** 1999. Prevalence of antimicrobial resistance in respiratory tract isolates of *Streptococcus pneumoniae*: results of a Canadian national surveillance study. Antimicrob. Agents Chemother. **43:**2504–2509.
38. **Zhanel, G. G., M. Dueck, D. J. Hoban, L. Vercaigne, J. Embil, A. S. Gin, and J. A. Karlowsky.** 2001. Macrolides and ketolides: a review focusing on respiratory infections. Drugs **61:**443–498.
39. **Zhanel, G. G., and J. A. Karlowsky.** 2001. Ribosomal resistance: emerging problems and potential solutions. Curr. Infect. Dis. Rep. **1:**459–463.
40. **Zhanel, G. G., K. Ennis, L. Vercaigne, A. Walkty, A. S. Gin, J. Embil, H. Smith, and D. J. Hoban.** 2002. The new fluoroquinolones: focus on respiratory infections. Drugs **62:**13–59.