

DECREASED SUSCEPTIBILITY OF *STREPTOCOCCUS PNEUMONIAE*
TO FLUOROQUINOLONES IN CANADADANNY K. CHEN, M.D., ALLISON MCGEER, M.D., JOYCE C. DE AZAVEDO, PH.D., AND DONALD E. LOW, M.D.,
FOR THE CANADIAN BACTERIAL SURVEILLANCE NETWORK***ABSTRACT**

Background Fluoroquinolones are now recommended for the treatment of respiratory tract infections due to *Streptococcus pneumoniae*, particularly when the isolates are resistant to β -lactam antibiotics. Although pneumococci with reduced susceptibility to fluoroquinolones have been identified, their prevalence has not been determined in a defined population.

Methods We performed susceptibility testing on 7551 isolates of *S. pneumoniae* obtained from surveillance in Canada in 1988 and from 1993 to 1998. Pneumococci with reduced susceptibility to fluoroquinolones (defined as a minimal inhibitory concentration of ciprofloxacin of at least 4 μ g per milliliter) were further characterized. We also examined antibiotic prescriptions dispensed in Canadian retail pharmacies.

Results Between 1988 and 1997, fluoroquinolone prescriptions increased from 0.8 to 5.5 per 100 persons per year. The prevalence of pneumococci with reduced susceptibility to fluoroquinolones increased from 0 percent in 1993 to 1.7 percent in 1997 and 1998 ($P=0.01$). Among adults, the prevalence increased from 1.5 percent in 1993 and 1994 combined to 2.9 percent in 1997 and 1998 combined. The prevalence was higher in isolates from older patients (2.6 percent among those 65 years of age or older vs. 1.0 percent among those 15 to 64 years of age, $P<0.001$) and among those from Ontario (1.5 percent, vs. 0.4 percent among those from the rest of Canada; $P<0.001$). Fluoroquinolone use was greatest among the elderly and in Ontario. The 75 isolates (17 serotypes) of pneumococci with reduced susceptibility to fluoroquinolones were submitted by 40 laboratories in eight provinces. Reduced susceptibility to fluoroquinolones was associated with resistance to penicillin.

Conclusions The prevalence of pneumococci with reduced susceptibility to fluoroquinolones is increasing in Canada, probably as a result of selective pressure from the increased use of fluoroquinolones. (N Engl J Med 1999;341:233-9.)

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S*TREPTOCOCCUS pneumoniae* is the most common bacterial cause of community-acquired pneumonia, meningitis, otitis media, and sinusitis. The emergence of resistance to antimicrobial agents commonly used for the treatment of pneumococcal disease has led to changes in recommended regimens of antimicrobial treat-

ment.¹⁻⁵ The earlier fluoroquinolones, including norfloxacin, ciprofloxacin, and ofloxacin, have borderline activity against pneumococci at the recommended dosages and therefore are not recommended for the treatment of pneumococcal infections.⁶ However, with the increase in the use of ciprofloxacin and the introduction of newer fluoroquinolones such as levofloxacin, grepafloxacin, and trovafloxacin that have greater in vitro activity against *S. pneumoniae*, these agents are now being recommended for the treatment of pneumococcal infections, including community-acquired pneumonia, acute bacterial exacerbations of chronic bronchitis, and sinusitis.⁷⁻⁹

Although there is increasing evidence that antimicrobial resistance is directly related to increased use, some question the need for concern about the fluoroquinolones, since after 15 years of clinical use, there have been only occasional reports of pneumococci with reduced susceptibility.^{4,10-13} However, the development of reduced susceptibility to fluoroquinolones requires sequential mutations, and one might thus expect a substantial delay between the introduction of fluoroquinolones and the appearance of clinically significant reductions in susceptibility.¹⁴⁻¹⁷ To determine whether the susceptibility of pneumococci to fluoroquinolones has changed in Canada, we systematically examined pneumococcal isolates collected by the Canadian Bacterial Surveillance Network between 1988 and 1998.

METHODS

Members of the Canadian Bacterial Surveillance Network, which consists of private laboratories and community and university-affiliated hospitals in all 10 provinces in Canada, were asked to collect the first 20 consecutive clinical isolates and then all sterile-site isolates of *S. pneumoniae* in 1988 and from October 1993 through September 1998. The date of collection, the source of the specimen, and the patient's age and sex were recorded on a standardized form. Duplicate isolates from the same patient were excluded.

The isolates were transported on chocolate-agar slants or swabs to a central laboratory. On receipt, the isolates were confirmed to be *S. pneumoniae* by standard methods. After storage at -70°C ,

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*The other members of the Canadian Bacterial Surveillance Network are listed in the Appendix.

the isolates were thawed and subcultured on blood agar twice before susceptibility testing was undertaken. In vitro susceptibility testing was performed by broth microdilution according to the guidelines of the National Committee for Clinical Laboratory Standards.¹⁸ To determine the minimal inhibitory concentration (MIC) for each isolate, the following concentrations of antimicrobial agents (in micrograms per milliliter) were tested, with the use of doubling dilutions: penicillin G, 0.03 to 8; ciprofloxacin, 0.06 to 64; gatifloxacin, 0.06 to 32; grepafloxacin, 0.06 to 32; levofloxacin, 0.06 to 64; sparfloxacin, 0.06 to 64; trovafloxacin, 0.06 to 32; moxifloxacin, 0.03 to 32; gemifloxacin, 0.03 to 32; erythromycin, 0.12 to 16; clindamycin, 0.25 to 16; tetracycline, 1 to 32; trimethoprim-sulfamethoxazole, 0.25 to 128 (trimethoprim component); and chloramphenicol, 2 to 16. The antimicrobial agents were supplied by their manufacturers.

Pneumococci with reduced susceptibility to fluoroquinolones were defined as those for which the MIC of ciprofloxacin was at least 4 µg per milliliter. This degree of resistance is associated with mutations in the fluoroquinolone-resistance-determining regions of genes encoding DNA topoisomerase IV (*parC*) and DNA gyrase A (*gyrA*).^{14,16,17} Moreover, this MIC is above the usual peak serum concentration of ciprofloxacin. The isolates were classified as susceptible to penicillin (MIC, ≤0.06 µg per milliliter), of intermediate susceptibility to penicillin (MIC, >0.06 to <2.0 µg per milliliter), or resistant to penicillin (MIC, ≥2.0 µg per milliliter). The interpretive standards for MICs of the National Committee for Clinical Laboratory Standards were also used to classify pneumococcal isolates as susceptible, of intermediate susceptibility, or resistant to the other antimicrobials tested.¹⁸ Because of the relatively small numbers of isolates in 1993 and 1998, in some places we report combined data for 1993 and 1994 and for 1997 and 1998.

All isolates with MICs of ciprofloxacin of at least 4 µg per milliliter were serotyped by the National Reference Center for Streptococcus (Edmonton, Alta.) with the use of type-specific antiserum.¹⁹ The genomic DNA of two groups of 12 and 14 randomly chosen isolates with MICs of ciprofloxacin of 1 µg per milliliter and 2 µg per milliliter, respectively, as well as all isolates with MICs of ciprofloxacin of at least 4 µg per milliliter, were examined by pulsed-field gel electrophoresis after digestion with *Sma*I in order to clarify clonal relationships.^{20,21} These isolates were further characterized by polymerase-chain-reaction and restriction-fragment-length polymorphism analysis with *Hinf*I for the most commonly recognized mutations in *parC* and *gyrA* associated with resistance to fluoroquinolones that have previously been described in *Staphylococcus aureus* and *Escherichia coli*.^{22,23}

Differences in group proportions were assessed with the chi-square test or Fisher's exact test. The Wilcoxon rank-sum test or single-factor analysis of variance was used for comparison of means. Multivariate logistic-regression modeling with SAS software (version 6.12, SAS Institute, Cary, N.C.) was used to test the associations in isolates of pneumococci between reduced susceptibility to fluoroquinolones and other characteristics of the isolates. Variables in the logistic-regression modeling included those associated with resistance in univariate analysis ($P < 0.10$).

IMS HEALTH, Canada, provided an estimate of the total number of antibiotic prescriptions dispensed in Canadian retail pharmacies based on a representative sample of 2000 pharmacies stratified according to type, size, and province. A representative sample of 652 office-based physicians stratified according to province and specialty was used to provide total estimated fluoroquinolone use according to age group. Demographic information based on national census data for the country and provinces was obtained from Statistics Canada.

RESULTS

Between 1988 and 1998, members of the Canadian Bacterial Surveillance Network submitted 7551 isolates of *S. pneumoniae* to the surveillance program. The number of participating centers was 15 in 1988,

24 in 1993, and from 42 to 141 between 1994 and 1998. Nineteen private laboratories serving physicians' offices and nursing homes submitted 1303 isolates (17 percent of the total), and 162 laboratories in hospitals (with a median of 360 beds per hospital and a range of 36 to 837) submitted the remaining 6248 (83 percent of the total). The median number of isolates submitted per center was 21 (range, 1 to 760).

Of the isolates, 2630 (35 percent) were from blood or other sterile sites (2411 from blood, 101 from cerebrospinal fluid, and 118 from other sterile fluids), 2769 (37 percent) were from the respiratory tract (1910 from sputum, 337 from bronchoscopic specimens, 246 from nasal or sinus specimens, 238 from pharyngeal specimens, and 38 from other respiratory tract specimens), and 2073 (27 percent) were from other sites (1482 from eye swabs, 522 from ear swabs, and 69 from other sites). The source of 79 isolates (1.0 percent) was not specified.

The patient's age was requested on surveillance forms in all years except 1988. The patient's age was provided for 6335 of 7551 isolates (84 percent); among these, 2311 specimens were from children under 15 years of age (36 percent), 2060 were from adolescents and adults 15 to 64 years of age (33 percent), and 1964 were from adults 65 years of age or older (31 percent).

Overall, 684 isolates (9.1 percent) were not susceptible to penicillin (resistant or of intermediate susceptibility). The prevalence of isolates that were not susceptible to penicillin increased from 2.4 percent (4 of 166) in 1988 to 13.9 percent (256 of 1844) in 1997 and 1998 combined. Over the same period, the rate of resistance to macrolides increased from 1.2 percent (2 of 166) to 6.7 percent (124 of 1844), resistance to trimethoprim-sulfamethoxazole increased from 1.8 percent (3 of 163) to 11.6 percent (207 of 1791), and resistance to tetracycline increased from 2.4 percent (4 of 166) to 6.9 percent (128 of 1844).

The overall prevalence of pneumococci with reduced susceptibility to fluoroquinolones was 1.0 percent (75 of 7551). The prevalence increased from 0 percent (0 of 327) in 1988 and 1993 to 1.7 percent (32 of 1844) in 1997 and 1998 ($P = 0.01$). No pneumococci with reduced susceptibility to fluoroquinolones were obtained from children. Among adults, the prevalence increased from 1.5 percent (24 of 1566) in 1993 and 1994 combined to 2.9 percent (29 of 1016) in 1997 and 1998 combined. The greatest change was seen among people 15 to 64 years of age, in whom the percentage of pneumococcal isolates with reduced susceptibility to fluoroquinolones increased from 0.5 percent (4 of 833) in 1993 and 1994 to 2.0 percent (10 of 492) in 1997 and 1998 (Fig. 1). The prevalence of pneumococci with reduced susceptibility to fluoroquinolones was higher in isolates from elderly patients (2.6 percent

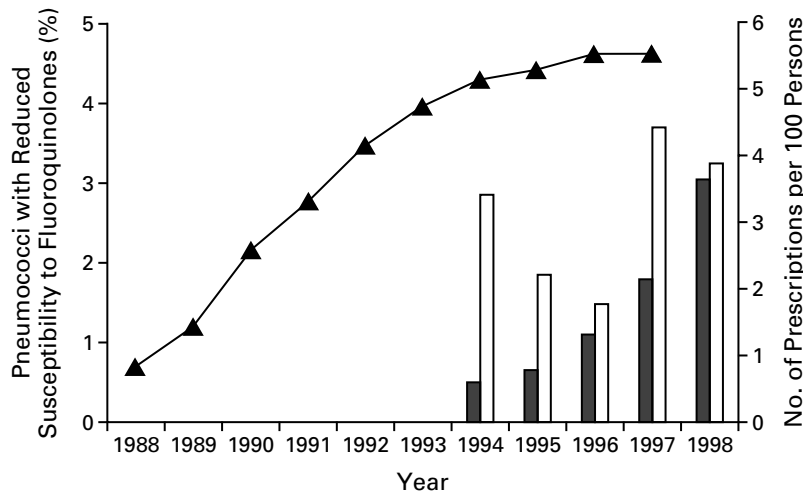


Figure 1. Fluoroquinolone Prescriptions per Capita (Curve) and Frequency of Pneumococci with Reduced Susceptibility to Fluoroquinolones in Canada According to the Patient's Age (Bars).

No isolates with reduced susceptibility were identified for persons who were younger than 15 years. Solid bars indicate an age of 15 to 64 years, and open bars an age of 65 years or older. Data on per capita fluoroquinolone prescriptions were obtained from 1988 through 1997, and data on the frequency of pneumococci with decreased susceptibility to fluoroquinolones in each age group were obtained in 1988 and in 1993 through 1998. No isolates with reduced susceptibility were identified in 1988 or 1993.

[51 of 1964] in those 65 years of age or older, as compared with 1.0 percent [20 of 2060] in those 15 to 64 years of age; $P < 0.001$) and in those from Ontario (1.5 percent [60 of 4090], vs. 0.4 percent [15 of 3461] among those from the rest of Canada; $P < 0.001$). These findings were consistent in all years for which data were available.

Overall, the number of fluoroquinolone prescriptions increased from 0.8 to 5.5 per 100 persons per year between 1988 and 1997 (Fig. 1). Per capita fluoroquinolone use was greatest among the elderly and in Ontario. Between 1993 and 1997 the number of fluoroquinolone prescriptions ranged from 13 to 18 per 100 persons per year among people 65 or older. In the province of Ontario, there was an increase from less than 1 per 100 in 1988 to 6.8 per 100 in 1997. In addition to the increase in the prevalence of pneumococci with reduced susceptibility to fluoroquinolones, the degree of reduction in susceptibility to fluoroquinolones also changed. From 1994 to 1998, there was a statistically significant increase in the proportion of isolates with an MIC of ciprofloxacin of at least 32 μg per milliliter ($P = 0.04$).

The 75 pneumococcal isolates with reduced susceptibility to fluoroquinolones were obtained from 40 different laboratories (38 hospital-based and 2 private) located in eight provinces. Seventeen different serotypes were identified among 73 isolates successfully serotyped. The most frequent serotypes were 11A (nine isolates); 23F (eight isolates); 9V (seven

isolates); 6A, 6B, and 9N (six isolates each); 22F (five isolates); and 14 (four isolates). With the exception of two serotype 3 isolates with the same electrophoretic pattern identified from the same laboratory in the same year, serotyping and pulsed-field gel electrophoresis revealed no clustering of pneumococci with reduced susceptibility to fluoroquinolones. The 10 isolates with MICs of ciprofloxacin of at least 32 μg per milliliter were 3 isolates of serotype 11A (2 clonally related according to electrophoresis), 2 of serotype 19F (clonally distinct according to electrophoresis), and 1 each of serotypes 6A, 6B, 9V, 18A, and 19A.

The increases in the MIC of ciprofloxacin were paralleled by increases in the MICs of the other fluoroquinolones. In general, the newer fluoroquinolones had MICs that were lower than that of ciprofloxacin by a factor of at least four, with gemifloxacin having the greatest in vitro activity against *S. pneumoniae* (Table 1). Mutations in the fluoroquinolone-resistance-determining region of the *parC* and *gyrA* genes encoding subunits of topoisomerase IV and DNA gyrase A have been found in isolates with decreased susceptibility to fluoroquinolones.²² After *Hinf*I restriction-fragment-length polymorphism analysis, 12 randomly chosen isolates with MICs of ciprofloxacin of no more than 1 μg per milliliter did not have evidence of mutations at the key Asp80-Ser81 (*gyrA*) or Asp78-Ser79 (*parC*) loci. In contrast, 5 of 14 isolates associated with MICs of ciprofloxacin of 2 μg per milliliter (36 percent), 21 of 41

TABLE 1. IN VITRO ACTIVITY OF SELECTED FLUOROQUINOLONES AGAINST 75 PNEUMOCOCCAL ISOLATES WITH MICs OF CIPROFLOXACIN OF $\geq 4 \mu\text{g}$ PER MILLILITER COLLECTED IN CANADA FROM 1994 THROUGH 1998.

FLUOROQUINOLONE	MINIMAL INHIBITORY CONCENTRATION ($\mu\text{g/ml}$)*											
	≤ 0.03	0.06	0.12	0.25	0.5	1.0	2.0	4.0	8.0	16.0	32.0	64.0
	no. of isolates inhibited (cumulative %)											
Ciprofloxacin								41 (55)	13 (72)	11 (87)	4 (92)	6 (100)
Levofloxacin				1 (1)	11 (16)	35 (63)	3 (67)	10 (80)	11 (95)	4 (100)		
Sparfloxacin			2 (3)	37 (52)	8 (63)	1 (64)	7 (73)	14 (92)	2 (95)	3 (99)	1 (100)	
Grepafloxacin			14 (19)	24 (51)	10 (64)	3 (68)	13 (85)	6 (93)	5 (100)			
Trovafloxacin			14 (19)	31 (60)	6 (68)	7 (77)	10 (91)	6 (99)	1 (100)			
Gatifloxacin			3 (4)	41 (59)	4 (64)	8 (75)	14 (93)	5 (100)				
Moxifloxacin			3 (4)	39 (56)	5 (63)	6 (71)	13 (88)	7 (97)	2 (100)			
Gemifloxacin	24 (32)	22 (61)	10 (75)	13 (92)	2 (95)	4 (100)						

*Values in boldface type are at the proposed or established intermediate interpretive standards for susceptibility as defined by the National Committee for Clinical Laboratory Standards.¹⁸

with MICs of $4 \mu\text{g}$ per milliliter (51 percent), 11 of 13 with MICs of $8 \mu\text{g}$ per milliliter (85 percent), and 21 of 21 with MICs of at least $16 \mu\text{g}$ per milliliter (100 percent) ($P < 0.001$) were found to have these mutations. The proportion of isolates with mutations demonstrable by *Hinf*I restriction-fragment-length polymorphism analysis in both *parC* and *gyrA* also increased with increasing MICs of ciprofloxacin. Twelve of 21 isolates associated with MICs of at least $16 \mu\text{g}$ per milliliter (57 percent) had these mutations in both *parC* and *gyrA*, as compared with 2 of 13 for which the MIC was $8 \mu\text{g}$ per milliliter (15 percent) and 1 of 41 for which the MIC was $4 \mu\text{g}$ per milliliter (2 percent) ($P < 0.001$).

According to univariate analysis, pneumococci with reduced susceptibility to fluoroquinolones were significantly more likely to be isolated from older patients, from respiratory tract specimens, from patients in the province of Ontario, and during the later years of surveillance (Table 2). Pneumococci with reduced susceptibility to fluoroquinolones were also significantly more likely to be resistant to penicillin (relative risk, 5.0; 95 percent confidence interval, 2.5 to 10), trimethoprim-sulfamethoxazole (relative risk, 3.9; 95 percent confidence interval, 2.2 to 7.0), and tetracycline (relative risk, 2.7; 95 percent confidence interval, 1.2 to 5.8). According to multivariate analysis, pneumococci with reduced susceptibility to fluoroquinolones were significantly more likely to be isolated from older patients, from respiratory tract specimens, from patients in Ontario, and during the later years of surveillance, and were also more likely to be resistant to penicillin (Table 3). Secondary analysis using only the 3278 isolates from laboratories that submitted isolates in all four years between 1994 and 1997 yielded the same associations as the primary analysis (data not shown).

DISCUSSION

This study provides evidence that the increase in the use of fluoroquinolones in Canada is associated with an increase in the frequency and degree of reduced susceptibility to fluoroquinolones among pneumococci, especially among penicillin-resistant *S. pneumoniae*. Previous studies have shown strong associations between the use of antimicrobial agents in the community and the emergence of antimicrobial resistance in a number of organisms.²⁴⁻²⁹ Our study demonstrates that the prevalence of pneumococci with reduced susceptibility to fluoroquinolones not only increased over time but also was associated with the age group (persons 65 or older) and geographic location (Ontario) with the highest per capita use of fluoroquinolones.

Pneumococci with reduced susceptibility to fluoroquinolones were reported by 40 of the participating laboratories. Serotyping and pulsed-field gel electrophoresis demonstrated that the pneumococci with reduced susceptibility to fluoroquinolones were of multiple clones and serotypes, suggesting that new resistance is developing in multiple indigenous strains. Together, these results further support the hypothesis that selective pressure applied to many strains simultaneously is the important determinant of the emergence of resistance. However, the increased prevalence of pneumococci with reduced susceptibility to fluoroquinolones might also result from clonal dissemination.³⁰ The dramatic increase in *S. pneumoniae* that are not susceptible to penicillin in Iceland, resulting from the spread of a serotype 6B clone, and the well-documented international dissemination of a multiresistant serotype 23F clone, serve as reminders of the efficiency with which a fit, resistant pneumococcal strain can spread.³¹⁻³⁵

Penicillin resistance is a marker for resistance to oth-

TABLE 2. FACTORS ASSOCIATED WITH REDUCED SUSCEPTIBILITY TO FLUOROQUINOLONES IN 7551 ISOLATES OF *STREPTOCOCCUS PNEUMONIAE*.

FACTOR	No. (%) WITH MIC OF CIPROFLOXACIN OF AT LEAST 4 µg/ml	P VALUE
Patient's age*		<0.001†
<15 yr	0/2311	
15–64 yr	20/2060 (0.9)	
≥65 yr	51/1964 (2.6)	
Source of isolate‡		0.001†
Blood or other sterile fluid§	24/2630 (0.9)	
Respiratory tract¶	45/2769 (1.6)	
Other	5/2073 (0.2)	
Geographic area		<0.001†
Atlantic Canada and Quebec	7/1379 (0.5)	
Ontario	60/4090 (1.5)	
Western Canada	8/2082 (0.4)	
Institution or offices served by laboratory		0.66**
Physicians' offices or nursing homes	11/1303 (0.8)	
Hospital	64/6248 (1.0)	
No. of beds in hospital served		0.11†
<200	9/1464 (0.6)	
200–349	14/1486 (0.9)	
>349	41/3298 (1.2)	
Year of isolation		0.008†
1988	0/166	
1993	0/161	
1994	24/2813 (0.9)	
1995	11/1505 (0.7)	
1996	8/1062 (0.8)	
1997	24/1400 (1.7)	
1998	8/444 (1.8)	
Penicillin resistance of isolate		0.002†
Susceptible	61/6867 (0.9)	
Intermediate	5/463 (1.1)	
Resistant	9/221 (4.1)	

*The patient's age was unknown in the case of 1216 isolates.

†The P value was calculated by the likelihood-ratio chi-square test.

‡The source was unknown for 79 isolates.

§There were 2411 isolates from blood, 101 from cerebrospinal fluid, and 118 from other sterile body fluids.

¶There were 1910 isolates from sputum, 337 from bronchoscopic specimens, 246 from nasal or sinus swabs, 238 from pharyngeal swabs, and 38 from other sites.

||There were 1482 isolates from eye swabs, 522 from ear swabs, and 69 from other specimens.

**The P value was calculated by Fisher's exact test.

er antimicrobial agents, including trimethoprim–sulfamethoxazole, erythromycin, and tetracycline.^{1,3-5,36,37} However, there are conflicting reports about the relation between penicillin resistance and reduced susceptibility to fluoroquinolones in *S. pneumoniae*.^{4,38-41} Our results suggest that the relation exists but may be difficult to detect, because β-lactam use is highest among children, whereas fluoroquinolones are used mainly by adults. This association is of particular concern, since the current and future fluoroquinolones with enhanced activity against *S. pneumoniae* will be targeted for use against infections due to penicillin-resistant *S. pneumoniae*.^{8,9}

As with penicillin resistance, there can be both re-

TABLE 3. MULTIVARIATE ANALYSIS OF FACTORS ASSOCIATED WITH REDUCED SUSCEPTIBILITY TO FLUOROQUINOLONES IN ISOLATES OF *STREPTOCOCCUS PNEUMONIAE*.

FACTOR	ADJUSTED OR (95% CI)*	P VALUE
Patient's age	1.6 (1.4–1.8)	<0.001
Year of isolation	1.2 (1.0–1.4)	0.05
Geographic area		
Atlantic Canada and Quebec†	1.0	
Ontario	4.6 (1.8–1.2)	<0.001
Western Canada	1.2 (0.4–3.9)	0.71
Source of isolate		
Blood or other sterile fluid†	1.0	
Respiratory tract	2.7 (1.6–4.8)	<0.001
Other	1.4 (0.5–3.8)	0.56
Degree of resistance to penicillin		
Susceptible†	1.0	
Intermediate	1.3 (0.5–3.5)	0.55
Resistant	3.7 (1.7–8.1)	<0.001

*OR denotes odds ratio, and CI confidence interval. Odds ratios were calculated per decade of life for age, and per year for year of isolation.

†This was the reference group.

gional and temporal variation in the prevalence of pneumococci with reduced susceptibility to fluoroquinolones.⁴²⁻⁴⁶ Participation in the Canadian Bacterial Surveillance Network is voluntary, and the participation of specific centers varies from year to year. Therefore, these data cannot be used to examine detailed regional differences, and the Canadian population is not fully represented. However, the consistency of identified associations in the secondary analysis and the fact that the rates of penicillin resistance in this system are very similar to those reported by other Canadian surveillance systems support the data presented.¹⁰ Nonetheless, these data need to be confirmed in studies of surveillance data from other geographic areas, and ongoing surveillance is required to assess the evolution of pneumococci with reduced susceptibility to fluoroquinolones in Canada and in other countries.

Further increases in both the prevalence and the degree of reduced susceptibility to fluoroquinolones can be anticipated if fluoroquinolone use continues to increase. As the prevalence of penicillin-resistant pneumococci and multiresistant strains has increased, there has been a growing impetus to use fluoroquinolones in children, who are major reservoirs of pneumococci. The potential role of fluoroquinolones in pediatric infections has long been under consideration.⁴⁷ Studies approved by the Food and Drug Administration are currently investigating the use of newer fluoroquinolones in children (McCracken GH Jr: personal communication). Clinical isolates associated with MICs of newer fluoroquinolones of at least 8 µg per milliliter have already been described.^{13,48,49}

If the value of this important group of antimicrobial agents is to be preserved, it is essential not only to control their inappropriate use but also to learn which fluoroquinolones, and which doses and durations of therapy, will minimize the selection of resistant bacteria.⁵⁰⁻⁵²

Supported in part by a grant from the Canadian Bacterial Diseases Network.

APPENDIX

Other investigators of the Canadian Bacterial Surveillance Network are as follows: C. Duncan, L. Trpeski, D. Libertucci, S. Pong-Porter, and D. Bast (Mount Sinai Hospital, Toronto); R. Davidson and K. Forward (Queen Elizabeth II Health Sciences Centre, Halifax, N.S.); L. Mandell (McMaster University, Hamilton, Ont.); A. Simor (Sunnybrook Health Science Centre, Toronto); D. Hoban and G. Zhanel (University of Manitoba, Winnipeg); M. Laverdiere and K. Weiss (Hôpital Maisonneuve-Rosemont, University of Montreal, Montreal); L. Abbott (Queen Elizabeth Hospital, Charlottetown, P.E.I.); J. Blondeau (St. Paul's Hospital and University of Saskatchewan, Saskatoon); G. Murray (Centre Hospitalier Universitaire de Québec St. Sacrement, Sainte Foy); G. Randhawa (Kelowna General Hospital, Kelowna, B.C.); G. Harding and S. Hoban (St. Boniface General Hospital, Winnipeg, Man.); D. Hinds (Richmond Hospital, Richmond, B.C.); C. Gaudreau (Campus Saint-Luc, Centre Hospitalier de l'Université de Montréal, Montreal); R. Roy (Vernon Jubilee Hospital, Vernon, B.C.); D. Groves (St. Joseph's Hospital, Hamilton, Ont.); M. Bergeron (Université Laval, Quebec, Que.); D. Gregson (St. Joseph's Health Centre, London, Ont.); P. Jessamine and B. Toye (Ottawa Civic Hospital and Ottawa General Hospital, Ottawa, Ont.); P. Kibsey (Victoria General Hospital, Victoria, B.C.); R. Rennie, University of Alberta Hospitals, Edmonton); P. Turgeon (Hôpital Saint-Luc and Université de Montréal, Montreal); P. Leighton (Dr. Everett Chalmers Hospital, Fredericton, N.B.); L. Thibault (Dr. Georges L. Dumont Hospital, Moncton, N.B.); M. Kuhn (Moncton Hospital, Moncton, N.B.); R. Lewis (Cape Breton Regional Hospital, Sydney, N.S.); P. Jutras (Centre Hospitalier Régional de Rimouski, Rimouski, Que.); D. Church (Calgary Laboratory Services, Calgary, Alta.); J. Nigrin, E. Blondell-Hill, and J. Galbraith (DynaCare Kasper Medical Laboratories, Edmonton, Alta.); M. Lovgren (National Centre for Streptococcus, Edmonton, Alta.); and J.M. Hutchinson (Health Sciences Centre, St. John's, Newf.).

REFERENCES

- Doern GV, Pfaller MA, Kugler K, Freeman J, Jones RN. Prevalence of antimicrobial resistance among respiratory tract isolates of *Streptococcus pneumoniae* in North America: 1997 results from the SENTRY antimicrobial surveillance program. *Clin Infect Dis* 1998;27:764-70.
- Rahal K, Wang F, Schindler J, et al. Reports on surveillance of antimicrobial resistance in individual countries. *Clin Infect Dis* 1997;24:Suppl 1: S169-S175.
- Butler JC, Hofmann J, Cetron MS, Elliott JA, Facklam RR, Breiman RF. 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* 1996;174:986-93.
- Gruneberg RN, Felmingham D. Results of the Alexander Project: a continuing, multicenter study of the antimicrobial susceptibility of community-acquired lower respiratory tract bacterial pathogens. *Diagn Microbiol Infect Dis* 1996;25:169-81.
- Doern GV, Brueggemann A, Holley HP Jr, Rauch AM. Antimicrobial resistance of *Streptococcus pneumoniae* recovered from outpatients in the United States during the winter months of 1994 to 1995: results of a 30-center national surveillance study. *Antimicrob Agents Chemother* 1996;40: 1208-13.
- Lee BL, Kimbrough RC, Jones SR, Chaisson RE, Mills J. Infectious complications with respiratory pathogens despite ciprofloxacin therapy. *N Engl J Med* 1991;325:520-1.
- Chodosh S, Schreurs A, Siami G, et al. Efficacy of oral ciprofloxacin vs. clarithromycin for treatment of acute bacterial exacerbations of chronic bronchitis. *Clin Infect Dis* 1998;27:730-8.
- Bartlett JG, Breiman RF, Mandell LA, File TM Jr. Community-acquired pneumonia in adults: guidelines for management: the Infectious Diseases Society of America. *Clin Infect Dis* 1998;26:811-38.
- Campbell GD Jr. Commentary on the 1993 American Thoracic Society guidelines for the treatment of community-acquired pneumonia. *Chest* 1999;115:Suppl 3:14S-18S.
- Simor AE, Louie M, Low DE. Canadian national survey of prevalence of antimicrobial resistance among clinical isolates of *Streptococcus pneumoniae*: Canadian Bacterial Surveillance Network. *Antimicrob Agents Chemother* 1996;40:2190-3.
- Richard MP, Aguado AG, Mattina R, Marre R. Sensitivity to sparflaxacin and other antibiotics, of *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* strains isolated from adult patients with community-acquired lower respiratory tract infections: a European multicentre study: SPAR Study Group: Surveillance Programme of Antibiotic Resistance. *J Antimicrob Chemother* 1998;41:207-14.
- Barry AL, Fuchs PC, Allen SD, Brown SD, Jorgensen JH, Tenover FC. In-vitro susceptibility of *Streptococcus pneumoniae* to the d- and l-isomers of ofloxacin: interpretive criteria and quality control limits. *J Antimicrob Chemother* 1996;37:365-9.
- Ballou CH, Jones RN, Johnson DM, Deinhart JA, Schentag JJ. Comparative in vitro assessment of sparflaxacin activity and spectrum using results from over 14,000 pathogens isolated at 190 medical centers in the USA: SPAR Study Group. *Diagn Microbiol Infect Dis* 1997;29:173-86.
- Janoir C, Zeller V, Kitzis MD, Moreau NJ, Gutmann L. High-level fluoroquinolone resistance in *Streptococcus pneumoniae* requires mutations in parC and gyrA. *Antimicrob Agents Chemother* 1996;40:2760-4.
- Hooper DC. Bacterial topoisomerases, anti-topoisomerases, and anti-topoisomerase resistance. *Clin Infect Dis* 1998;27:Suppl 1:S54-S63.
- Tankovic J, Perichon B, Duval J, Courvalin P. Contribution of mutations in gyrA and parC genes to fluoroquinolone resistance of mutants of *Streptococcus pneumoniae* obtained in vivo and in vitro. *Antimicrob Agents Chemother* 1996;40:2505-10.
- Munoz R, De La Campa AG. ParC subunit of DNA topoisomerase IV of *Streptococcus pneumoniae* is a primary target of fluoroquinolones and cooperates with DNA gyrase A subunit in forming resistance phenotype. *Antimicrob Agents Chemother* 1996;40:2252-7.
- Performance standards for antimicrobial susceptibility testing: eighth informational supplement. NCCLS document M100-SB. Wayne, Pa.: National Committee for Clinical Laboratory Standards, 1998.
- Lovgren M, Spika JS, Talbot JA. Invasive *Streptococcus pneumoniae* infections: serotype distribution and antimicrobial resistance in Canada, 1992-1995. *CMAJ* 1998;158:327-31.
- Murray BE, Singh KV, Heath JD, Sharma BR, Weinstock GM. Comparison of genomic DNAs of different enterococcal isolates using restriction endonucleases with infrequent recognition sites. *J Clin Microbiol* 1990;28:2059-63. [Erratum, *J Clin Microbiol* 1991;29:418.]
- Tenover FC, Arbeit RD, Goering RV, et al. Interpreting chromosomal DNA restriction patterns produced by pulsed-field gel electrophoresis: criteria for bacterial strain typing. *J Clin Microbiol* 1995;33:2233-9.
- Pan XS, Ambler J, Mehtar S, Fisher LM. Involvement of topoisomerase IV and DNA gyrase as ciprofloxacin targets in *Streptococcus pneumoniae*. *Antimicrob Agents Chemother* 1996;40:2321-6.
- Sreedharan S, Peterson LR, Fisher LM. Ciprofloxacin resistance in coagulase-positive and -negative staphylococci: role of mutations at serine 84 in the DNA gyrase A protein of *Staphylococcus aureus* and *Staphylococcus epidermidis*. *Antimicrob Agents Chemother* 1991;35:2151-4.
- Arason VA, Kristinsson KG, Sigurdsson JA, Stefansdottir G, Molstad S, Gudmundsson S. Do antimicrobials increase the carriage rate of penicillin resistant pneumococci in children? Cross sectional prevalence study. *BMJ* 1996;313:387-91.
- Seppälä H, Nissinen A, Järvinen H, et al. Resistance to erythromycin in group A streptococci. *N Engl J Med* 1992;326:292-7.
- Brook I, Gober AE. Prophylaxis with amoxicillin or sulfisoxazole for otitis media: effect on the recovery of penicillin-resistant bacteria from children. *Clin Infect Dis* 1996;22:143-5.
- Reichler MR, Rakovsky J, Sobotova A, et al. Multiple antimicrobial resistance of pneumococci in children with otitis media, bacteremia, and meningitis in Slovakia. *J Infect Dis* 1995;171:1491-6.
- Duchin JS, Breiman RF, Diamond A, et al. High prevalence of multi-drug-resistant *Streptococcus pneumoniae* among children in a rural Kentucky community. *Pediatr Infect Dis J* 1995;14:745-50.
- Wang EEL, Kellner JD, Arnold S. Antibiotic-resistant *Streptococcus pneumoniae*: implications for medical practice. *Can Fam Physician* 1998;44: 1881-8.
- Hall LM. Application of molecular typing to the epidemiology of *Streptococcus pneumoniae*. *J Clin Pathol* 1998;51:270-4.
- Kristinsson KG, Hjalmarsdottir MA, Steingrimsson O. Increasing penicillin resistance in pneumococci in Iceland. *Lancet* 1992;339:1606-7.
- Soares S, Kristinsson KG, Musser JM, Tomasz A. Evidence for the introduction of a multiresistant clone of serotype 6B *Streptococcus pneumoniae* from Spain to Iceland in the late 1980s. *J Infect Dis* 1993;168:158-63.
- Munoz R, Coffey TJ, Daniels M, et al. Intercontinental spread of a multiresistant clone of serotype 23F *Streptococcus pneumoniae*. *J Infect Dis* 1991;164:302-6.

34. Stephenson J. Icelandic researchers are showing the way to bring down rates of antibiotic-resistant bacteria. *JAMA* 1996;275:175.
35. Coffey TJ, Berron S, Daniels M, et al. Multiply antibiotic-resistant *Streptococcus pneumoniae* recovered from Spanish hospitals (1988-1994): novel major clones of serotypes 14, 19F and 15E. *Microbiology* 1996;142:2747-57.
36. Breiman RF, Butler JC, Tenover FC, Elliott JA, Facklam RR. Emergence of drug-resistant pneumococcal infections in the United States. *JAMA* 1994;271:1831-5.
37. Thornsberry C, Ogilvie P, Kahn J, Mauriz Y. Surveillance of antimicrobial resistance in *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* in the United States in 1996-1997 respiratory season: the Laboratory Investigator Group. *Diagn Microbiol Infect Dis* 1997;29:249-57.
38. Fuchs PC, Barry AL, Brown SD. Susceptibility of multi-resistant *Streptococcus pneumoniae* to ciprofloxacin, ofloxacin and levofloxacin. *J Antimicrob Chemother* 1997;39:671-2.
39. Goldstein FW, Acar JF. Antimicrobial resistance among lower respiratory tract isolates of *Streptococcus pneumoniae*: results of a 1992-93 western Europe and USA collaborative surveillance study: the Alexander Project Collaborative Group. *J Antimicrob Chemother* 1996;38:Suppl A:71-84.
40. Goldsmith CE, Moore JE, Murphy PG, Ambler JE. Increased incidence of ciprofloxacin resistance in penicillin-resistant pneumococci in Northern Ireland. *J Antimicrob Chemother* 1998;41:420-1.
41. Goldsmith CE, Moore JE, Murphy PG. Pneumococcal resistance in the UK. *J Antimicrob Chemother* 1997;40:Suppl A:11-8.
42. Kam KM, Luey KY, Fung SM, Yiu PP, Harden TJ, Cheung MM. Emergence of multiple-antibiotic-resistant *Streptococcus pneumoniae* in Hong Kong. *Antimicrob Agents Chemother* 1995;39:2667-70.
43. Yoshida R, Kaku M, Kohno S, et al. Trends in antimicrobial resistance of *Streptococcus pneumoniae* in Japan. *Antimicrob Agents Chemother* 1995;39:1196-8.
44. Setchanova L. Clinical isolates and nasopharyngeal carriage of antibiotic-resistant *Streptococcus pneumoniae* in Hospital for Infectious Diseases, Sofia, Bulgaria, 1991-1993. *Microb Drug Resist* 1995;1:79-84.
45. Marchese A, Debbia EA, Arvigo A, Pesce A, Schito GC. Susceptibility of *Streptococcus pneumoniae* strains isolated in Italy to penicillin and ten other antibiotics. *J Antimicrob Chemother* 1995;36:833-7.
46. Mittermayer H, Jebelean C, Binder L, Haditsch M, Watschinger R. Antibiotic susceptibility of pneumococci isolated in Austria over a four-year period. *Eur J Clin Microbiol Infect Dis* 1996;15:817-20.
47. Douidar SM, Snodgrass WR. Potential role of fluoroquinolones in pediatric infections. *Rev Infect Dis* 1989;11:878-89.
48. Wise R, Andrews JM. The activity of grepafloxacin against respiratory pathogens in the UK. *J Antimicrob Chemother* 1997;40:Suppl A:27-30.
49. Wise R, Brenwald N, Gill M, Fraise A. *Streptococcus pneumoniae* resistance to fluoroquinolones. *Lancet* 1996;348:1660.
50. Hooper DC. Expanding uses of fluoroquinolones: opportunities and challenges. *Ann Intern Med* 1998;129:908-10.
51. Zhao X, Xu C, Domagala J, Drlica K. DNA topoisomerase targets of the fluoroquinolones: a strategy for avoiding bacterial resistance. *Proc Natl Acad Sci U S A* 1997;94:13991-6.
52. Dalhoff A, Heidtmann M, Obertegger S, Hesse D. Lack of in vivo emergence of resistance against Bay 12-8039 in *Staph. aureus* and *Strep. pneumoniae*. In: Program and abstracts of the Eighth International Congress on Infectious Diseases, Boston, May 15-18, 1998:124. abstract.