

A cross-Canada surveillance of antimicrobial resistance in respiratory tract pathogens

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OBJECTIVE: To determine the prevalence of antimicrobial resistance in clinical isolates of *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* from medical centres across Canada.

METHODS: Fifty laboratories from across Canada were asked to collect up to 25 consecutive clinical isolates of *S pneumoniae*, *H influenzae* and *M catarrhalis* at some time between September 1994 and May 1995, and then again between September and December of 1996. A total of 2364 *S pneumoniae*, 575 *H influenzae* and 200 *M catarrhalis* samples were collected. *H influenzae* and *M catarrhalis* isolates were tested for the production of beta-lactamase. *S pneumoniae* isolates were characterized as penicillin susceptible, intermediately resistant or high level penicillin-resistant. Minimal inhibitory concentrations (MICs) were determined using a microbroth dilution technique described by the National Committee of Clinical Laboratory Standards.

RESULTS: Between the two collection periods, there was a significant increase in highly penicillin-resistant *S pneumoniae* from 2.1% to 4.4% ($P < 0.05$) and an increase in intermediately penicillin-resistant strains from 6.4% to 8.9% ($P < 0.05$). A significant increase in high level penicillin-resistant *S pneumoniae* was noted among paediatric isolates. No significant difference in the susceptibilities of comparator agents was detected. A significant increase in the number of beta-lactamase producing *H influenzae*, 34% to 43% ($P < 0.05$) was observed. Ninety-five per cent of *M catarrhalis* isolates were beta-lactamase producers in both time periods.

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CONCLUSIONS: During the course of this study, the incidence of penicillin resistance in *S pneumoniae* doubled. As a result of this increase, infections due to this organism in sites where poor penetration of beta-lactam antibiotics occur may become increasingly difficult to manage.

Key Words: Antimicrobial resistance, Respiratory tract pathogens

Étude épidémiologique pancanadienne sur la résistance des organismes pathogènes respiratoires aux antimicrobiens

OBJECTIF : Déterminer la prévalence de la résistance aux antimicrobiens dans les isolats cliniques de *Streptococcus pneumoniae*, *Haemophilus influenzae* et *Moraxella catarrhalis* dans différents centres médicaux canadiens.

MÉTHODES : Cinquante laboratoires des quatre coins du Canada ont été invités à recueillir jusqu'à 25 isolats cliniques consécutifs de *S. pneumoniae*, *H. influenzae* et *M. catarrhalis* entre septembre 1994 et mai 1995, puis à nouveau entre septembre et décembre 1996. En tout, 2 364 isolats de *S. pneumoniae*, 575 de *H. influenzae* et 200 de *M. catarrhalis* ont été recueillis. Les spécimens de *H. influenzae* et de *M. catarrhalis* ont été soumis à des tests pour vérifier s'ils produisaient des bêta-lactamases. Les isolats de *S. pneumoniae* ont été jugés sensibles, moyennement résistants ou très résistants à la pénicilline. Les concentrations minimales inhibitrices (CMI) ont été calculées à l'aide d'une technique de microdilution décrite par le *National Committee of Clinical Laboratory Standards*.

RÉSULTATS : Entre les deux périodes de cueillette, on a noté une augmentation significative du nombre de souches de *S. pneumoniae* très résistantes à la pénicilline, qui est passée de 2,1 % à 4,4 % ($p < 0,05$) et une augmentation de 6,4 % à 8,9 % ($p < 0,05$) des souches moyennement résistantes à la pénicilline. Une augmentation significative des souches de *S. pneumoniae* très résistantes à la pénicilline a été notée parmi les spécimens pédiatriques. Aucune différence significative n'a été notée entre les agents de comparaison. Une augmentation significative du nombre de souches de *H. influenzae* productrices de bêta-lactamases a été observée, soit de 34 % à 43 % ($p < 0,05$). Quatre-vingt-quinze pour cent des isolats de *M. catarrhalis* étaient producteurs de bêta-lactamases pendant les deux périodes en question.

CONCLUSION : Durant l'étude, l'incidence de la résistance de *S. pneumoniae* à la pénicilline a doublé. Par conséquent, les infections attribuables à cet organisme, là où la pénétration des bêta-lactamines est faible, pourraient devenir plus difficiles à traiter.

Streptococcus pneumoniae, Haemophilus influenzae and Moraxella catarrhalis are the most common bacterial pathogens associated with upper respiratory tract infections in both children and adults (1,2). These pathogens are frequently the causative agents in community-acquired pneumonia, acute sinusitis, acute exacerbation of chronic bronchitis, otitis media and meningitis. Worldwide increases in antimicrobial resistance and the changing epidemiology of pathogenic strains have required a change in the approach to treatment of infections due to these organisms.

Because rapid, sensitive and specific diagnostic tests are not available for the common respiratory bacterial pathogens, choice of antimicrobial therapy is nearly always empirical. Thus, it is essential to monitor rates of resistance to such pathogens so that the most efficacious agent can be used.

The present study was performed to determine the rates of antimicrobial resistance to three respiratory tract pathogens from across Canada. Centres that had previously provided isolates to determine resistance rates in various pathogens were asked to participate in the present study. Specifically, the rates of penicillin susceptibility in *S pneumoniae* and beta-lactamase production in *H influenzae* and *M catarrhalis* were determined. As well, the in vitro activities of selected antimicrobial agents were determined against all three pathogens.

METHODS

Fifty laboratories from across Canada were asked to collect up to 25 consecutive clinical isolates of *S pneumoniae*, *H influenzae* and *M catarrhalis* at some time between September 1994 and May 1995, and then again between September and

December of 1996. A total of 2364 *S pneumoniae*, 575 *H influenzae* and 200 *M catarrhalis* samples were collected. Almost all centres were tertiary care centres that served urban areas. All isolates were sent to Mount Sinai Hospital (Toronto, Ontario) microbiology laboratory for analysis. All isolates were nonsterile respiratory tract specimens that were predominately sputum cultures (greater than 90%). Only single isolates from different patients were included in the study. Study sites were asked to provide information on the patient's age and site of isolation. Isolates were identified using standard criteria (3). *H influenzae* were serotyped to determine whether they were type b using a commercial latex agglutination serotyping kit (Difco Laboratories, Michigan).

H influenzae and *M catarrhalis* isolates were tested for the production of beta-lactamase by the cefinase disk method (Becton Dickinson Microbiology Systems, Maryland) (4). Minimal inhibitory concentrations (MICs) were determined using a microbroth dilution technique described by the National Committee of Clinical Laboratory Standards (NCCLS) (Villanova, Pennsylvania) (5). The susceptible, intermediate and resistant breakpoints for determining penicillin susceptibility of *S pneumoniae* were: susceptible 0.06 mg/L or less, intermediate 0.12 to 1 mg/L and resistant 2.0 mg/L or greater. The following antimicrobials were evaluated: cefprozil (Cefzil, Bristol-Myers Squibb Canada Inc), cefaclor (Ceclor, Eli Lilly Canada Inc), cefixime (Suprax, Rhône-Poulenc Rorer Canada Inc), cephalixin (Keflex, Eli Lilly Canada Inc), cefuroxime (Zinacef, Glaxo Wellcome Canada Inc), ampicillin, clarithromycin (Biaxin, Abbott), azithromycin (Zithromax, Pfizer Canada), erythromycin and ciprofloxacin (Cipro, Bayer Inc). Erythromy-

TABLE 1
Penicillin susceptibility of 1320 strains of *Streptococcus pneumoniae* collected from across Canada between September 1994 and May 1995, and of 1044 strains in 1996

Province	Penicillin susceptibility category* (%)				
	Intermediate		Resistant		
	1994/95	1996	1994/95	1996	
Alberta/British Columbia	8 (5.9)	18 (16)	1 (0.7)	4 (3.5)	
North West Territories	8 (9.6)	6 (10.5)	3 (3.6)	2 (3.5)	
Saskatchewan	25 (18)	12 (14)	3 (2.2)	6 (7.1)	
Manitoba	4 (5.3)	12 (7.1)	1 (1.3)	9 (5.4)	
Ontario	30 (4.6)	39 (8.4)	15 (2.3)	21 (4.5)	
Quebec	5 (6.5)	2 (2.1)	4 (5.2)	3 (3.2)	
Maritime*	5 (3.2)	4 (6.3)	1 (0.6)	1 (1.6)	
Total	85 (6.4)	93 (8.9)	28 (2.1)	46 (4.4)	

*Maritime includes Newfoundland and Labrador, Nova Scotia, Prince Edward Island and New Brunswick. Intermediate Penicillin-intermediate minimum inhibitory concentration 0.1 to 1.0 mg/L; Resistant Resistant minimum inhibitory concentration 2.0 mg/L or greater

TABLE 2
In vitro activity of selected antimicrobial agents against *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis*

Antimicrobial	MIC _{90s} (mg/L) (percentage resistant)*						
	Total n=2364	<i>S pneumoniae</i>		<i>H influenzae</i>		<i>M catarrhalis</i>	
		Intermediate n=178	Resistant n=74	β-lac – n=361	β-lac + n=214	β-lac – n=10	β-lac + n=190
Ampicillin	0.25	2	4	2 (0.7)	16 (96)	0.12 (0)	16 (88.4)
Cefprozil	2.0	8	>16	8 (0)	8 (2.6)	0.5 (0)	4 (0)
Cefaclor	2	>16	>16	8 (0)	16 (11.8)	0.25 (0)	2 (0)
Cefixime	2.0	16	>16	0.25 (0)	0.25 (0)	0.25 (0)	0.5 (0)
Cephalexin	4	>16	>16	16	16	4	8
Cefuroxime	2.0 (12.3)	4 (42.4)	8 (100)	1 (0)	1 (0)	ND	ND
Ceftriaxone	0.25 (0.5)	0.5 (0.6)	2 (12)	ND	ND	ND	ND
Ciprofloxacin	1	2	2	0.06 (0)	0.06 (0)	0.06 (0)	0.06 (0)
Erythromycin	0.25 (4.3)	8 (12.9)	4 (18.7)	8	8	0.25 (0)	0.25 (0)
Clindamycin	0.25 (0.7)	0.25 (7.3)	0.5 (8)	ND	ND	ND	ND
TMP/SMX [†]	4 (9.5)	8 (65.6)	8 (86.7)	0.25 (2.9)	4 (13.7)	0.25 (0)	0.5 (0)
Tetracycline	2 (2.2)	2 (11.2)	16 (18.7)	2 (0)	2 (1.3)	ND	ND
Chloramphenicol	4 (1.0)	4 (3.9)	16 (14.7)	2 (0)	2 (0)	ND	ND

*When interpretive criteria available; [†]Trimethoprim/sulfamethoxazole (TMP/SMX) minimum inhibitory concentration (MIC) represented as trimethoprim. β-lac + Beta-lactamase positive; β-lac – Beta-lactamase negative; Intermediate Penicillin intermediate MIC 0.1 to 1.0 mg/L; ND Not done; Resistant Resistant MIC 2.0 mg/L or greater

cin, ampicillin, clindamycin, tetracycline, chloramphenicol, and trimethoprim/sulphamethoxazole (TMP/SMX) were obtained from Sigma Chemical Company (Michigan).

RESULTS

Of 3139 clinical isolates, *S pneumoniae* accounted for 75% (2364) of the isolates, 18.5% (575) were *H influenzae*, and the remaining 6.5% (or should be 6%) (200) were *M catarrhalis*. More than 90% of specimens were isolated from sputum samples.

Overall, approximately 40% of the *S pneumoniae* isolates were from a paediatric (age birth to 16 years) population, and 60% originated from adults during both time periods. In 1994-95, 91.4% of *S pneumoniae* strains were penicillin susceptible, 6.4% were intermediately resistant and 2.1% were highly resistant to penicillin (Table 1). In 1996, there was an

overall significant increase in intermediately resistant strains (8.9%) and highly resistant strains (4.4%) ($P < 0.05$). Most provinces had an increase in the number of intermediately and highly resistant *S pneumoniae* isolates (Table 1). No significant increases in intermediately or highly resistant *S pneumoniae* were observed in the adult population between 1994-95 and 1996, including those older than 65 years of age ($P > 0.05$). Significant increases were seen, however, in the paediatric population for both intermediately and highly resistant *S pneumoniae*. The prevalence of penicillin-resistant *S pneumoniae* in children increased from 1.8% in 1994-95 to 6.2% in 1996 ($P < 0.05$).

All agents tested had excellent activity against penicillin-susceptible strains. Among intermediately resistant strains, high rates of resistance were observed for erythromycin (12.9%), TMP/SMX (65.6%), cefuroxime (42.4%) and tetracy-

cline (11.2%) (Table 2). The incidence of clindamycin and chloramphenicol resistance was 7.3% and 3.9%, respectively. Rates of resistance for the cephalosporins were only calculated for cefuroxime and ceftriaxone because these are the only agents tested for which the NCCLS has established breakpoints for *S pneumoniae*. The same trend was seen in highly resistant strains. Significant increases in resistance were observed for cefuroxime (56%), erythromycin (18.7%), TMP/SMX (86.7%), ceftriaxone (12%) and chloramphenicol (20%).

Beta-lactamase was detected in 34% of *H influenzae* strains in 1994-95 and 43% in 1996. Of the 575 isolates that were collected, only three strains were serotype b. Two of these were isolated from adults and one from a child. Forty-four per cent of the *H influenzae* isolates were from a paediatric population, the remaining 56% were from adults.

For beta-lactamase negative *H influenzae*, all agents had good activity. Ninety-six per cent of beta-lactamase producing *H influenzae* were resistant to ampicillin, and 13.7% were resistant to TMP/SMX (Table 2). Among the oral cephalosporins, 11.8% displayed resistance to cefaclor, while only 2.6% were resistant to cefprozil. Low levels of tetracycline resistance (1.3%) were observed. No resistance was detected for cefuroxime, ciprofloxacin or chloramphenicol.

Beta-lactamase production was detected in 95% of the *M catarrhalis* isolates (Table 2). Seventy per cent of these isolates were from adults. The nonbeta-lactamase producing *M catarrhalis* isolates were sensitive to all agents tested. Predictably, the beta-lactamase producing *M catarrhalis* strains were resistant to ampicillin (88.4%). All other antimicrobials retained good activity against beta-lactamase-positive strains.

DISCUSSION

The management of patients with infections of the respiratory tract due to *H influenzae*, *S pneumoniae*, and *M catarrhalis* has been complicated by the emergence of antimicrobial resistance (6).

S pneumoniae remains the most common pathogen in acute community-acquired bacterial pneumonia, otitis media and sinusitis, and the second most common pathogen in bacterial meningitis (1,2). *S pneumoniae*, until 1967, had remained universally susceptible to penicillin, even though it was introduced into clinical practice in the 1940s. MICs were uniformly less than 0.01 mg/L. The first penicillin-resistant pneumococcal isolate was reported in 1967 in Australia (7). Resistance to penicillin was subsequently reported in South Africa and has now been encountered worldwide (8).

S pneumoniae with MICs to penicillin 0.1 mg/L or greater are considered nonsusceptible or resistant to penicillin. Resistance is further described as either intermediately or highly resistant. Intermediately resistant *S pneumoniae* have MICs to penicillin ranging from 0.1 to 1.0 mg/L. Highly resistant *S pneumoniae* have MICs greater than 1.0 mg/L. Before 1990, the prevalence of intermediately resistant *S pneumoniae* in Canada was reported to be approximately 1.5% (9,10). Highly resistant strains had not been reported. Significant increases in resistance to penicillin were first noted in 1993 (11). In a cross-Canada surveillance study performed during 1994 and

1995, 8.4% of isolates were intermediately resistant and 3.3% highly resistant to penicillin, results similar to our findings (12). Doern et al (13) reported that 14.1% and 9.5% of *S pneumoniae* isolates in the United States were intermediately and highly resistant to penicillin during the same time period. A more recent investigation reported that up to 36% of *S pneumoniae* isolates in the United States were resistant to penicillin (14). Our findings of the increasing prevalence of both intermediately and highly penicillin-resistant *S pneumoniae* reflects what is occurring in other parts of the world.

Beta-lactams bind to the penicillin-binding proteins (PBPs) of the organism, thereby inhibiting their function, which is the ongoing construction of new cell wall. Penicillin resistance is the result of the remodelling of the PBPs so that they have a decreased affinity for penicillin. This has occurred as the result of a combination of both chromosomal mutations and by exchange of a region encoding part of the penicillin-sensitive domain with a homologous region from a closely related species that produce forms of PBPs that are less susceptible to inhibition by the antibiotic (15,16). As remodelling occurs, the MIC increases in modest increments from sensitive to intermediate to resistant. The amount of remodelling and, therefore, the increase in level of penicillin resistance are limited because the function of the PBPs must be maintained in order for the organism to survive. By increasing the dose of the beta-lactam, effective therapy can be achieved for infections, such as bacteremia and pneumonia, where it is still possible to increase serum and tissue concentrations four- to eightfold dilutions above the MIC (17,18). However, at sites of infections where there is poor penetration of the beta-lactam, treatment failures can occur. The use of an oral beta-lactam antibiotic for the treatment of otitis media may not achieve the levels required to eradicate an infection by penicillin-resistant *S pneumoniae* (19). Even the use of high-dose parental penicillin for the treatment of meningitis may fail to achieve adequate concentrations in the cerebrospinal fluid (18).

Surveillance studies have shown that *S pneumoniae* strains that harbour penicillin resistance also tend to be resistant to other unrelated classes of antimicrobials. One study demonstrated that approximately 60% of penicillin-resistant *S pneumoniae* strains were resistant to at least one other drug (2). This increase in resistance is especially important for commonly used antimicrobials, such as TMP/SMX, the macrolides and the tetracyclines.

TMP/SMX is used extensively for the treatment of urinary tract, enteric and respiratory infections in developing countries. Trimethoprim selectively inhibits bacterial dihydrofolate reductase, thus preventing the reduction of dihydrofolate to tetrahydrofolate. Trimethoprim and TMP/SMX resistance has been strongly associated with penicillin resistance in *S pneumoniae*. Sixty-six per cent of intermediately resistant strains and 87% of highly resistant strains were resistant to TMP/SMX in the present study (Table 2). Resistance to TMP/SMX is defined as a MIC of 8 mg/L or greater. The mechanism of trimethoprim resistance is due to mutations to the dihydrofolate reductase genes (20). However, unlike penicillin resistance in *S pneumoniae*, the mutation results in a several fold increase

in the MIC to a trimethoprim level that is unachievable in serum and tissue.

The macrolides are the most often prescribed first-line therapy for community-acquired pneumonia (21). Macrolides (erythromycin and clarithromycin) and the azide, azithromycin, inhibit protein synthesis by binding to the 50S ribosomal subunits and inhibit elongation of peptide chains. Macrolide resistance in *S pneumoniae* is due primarily to the acquisition of a gene which is responsible for either efflux of the macrolide out of the cell or a gene which is responsible for modifying the ribosome so as to prevent antibiotic binding. Resistance is defined as a MIC of 0.5 mg/L or greater. The mean MICs for those strains resistant due to efflux is 10 mg/L and for those strains resistant due to ribosomal modification is 64 mg/L (22). Peak levels in serum of 2 to 3, 0.5 to 1, and 0.4 mg/L are reached at 3 h after oral doses of erythromycin (500 mg), clarithromycin (250 mg) and azithromycin (500 mg), respectively (23). Therefore, as with trimethoprim, the result of the development of resistance is a several fold increase in the MIC, well above achievable concentrations in the serum. As opposed to trimethoprim and TMP/SMX, this may, however, be offset by very high tissue concentrations of macrolides that are 10- to 100-fold higher than those in serum (24).

Before the introduction of the *H influenzae* serotype b (Hib) vaccine, Hib was a common and often fatal cause of infection (25,26). Dramatic declines in Hib-related disease in both children and adults have been observed since the introduction and widespread use of the vaccine. Scheifele et al (27) reported a decrease of more than 95% of Hib infections in children between 1985 and 1995. Our study found only three Hib strains in 575 isolates of *H influenzae*. Although nontypable *H influenzae* strains remain an important cause of mucosal disease in the respiratory tract in both children and adults, invasive disease is rare (26-29).

Before 1972, *H influenzae* was almost uniformly susceptible to ampicillin (30). During the 1970s, penicillin-resistant strains emerged due to the production of plasmid-mediated TEM-1 and ROB-1 beta-lactamases (31). PBPs with decreased affinity for beta-lactams have also been shown to confer resistance to penicillins and cephalosporins, although this occurred in less than 2% of *H influenzae* isolates tested in this

study (data not shown). In 1994, a cross-Canada surveillance study of *H influenzae* strains demonstrated that 37% of strains were beta-lactamase producers (32). The present study demonstrates that beta-lactamase resistance continues to increase significantly in *H influenzae*. In addition, there has been a disturbing increase in resistance rates to cefaclor, an antimicrobial that previously had been found to be relatively stable to the beta-lactamases of *H influenzae* (32).

M catarrhalis is recognized as a pathogen in otitis media, acute exacerbations of chronic bronchitis and sinusitis (33). Almost uniformly susceptible to beta-lactams before the 1980s, resistance due to beta-lactamase production is now in excess of 90% of isolates in most countries (2,33). Penicillin resistance in *M catarrhalis* is due to the production of two beta-lactamases, BRO-1 and BRO-2 (34,35). BRO-1 can be found in approximately 90% of isolates, and BRO-2 in the remaining 10%. Fortunately, *M catarrhalis* is a rare cause of invasive disease and plays a questionable role in mucosal disease (33).

Our findings of the increasing prevalence of penicillin resistance in *S pneumoniae* and beta-lactamase positivity in *H influenzae* are not surprising because doctors have not reduced the widespread use of oral antibiotics in the community, especially in children. To control resistance effectively in respiratory tract pathogens, regulating out-patient antimicrobial use is crucial (36,37). There are examples that, in some countries where resistance has emerged, efforts to control or reduce resistance have been successful. The emergence of macrolide resistance has been linked to widespread use of this antimicrobial class in Japan and Finland, and was controlled by policies that restricted macrolide use (38,39).

Canada's Laboratory Centre for Disease Control, Ottawa, Ontario and provincial governments have initiated multidisciplinary partnerships to reduce antimicrobial use. Our hopes of controlling antimicrobial resistance in Canada depend on both the success of these initiatives and the efforts of individual physicians.

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