Emergence of penicillin-resistant *Streptococcus pneumoniae* in southern Ontario, 1993-94

**ANDREW E SIMOR MD FRCPA, ANITA RACH LIS MD FRCPA, LISA LOUIE ART, JANET GOODFELLOW RT, MARIE LOUIE MD FRCPA**

**OBJECTIVE:** To determine the prevalence of resistance of *Streptococcus pneumoniae* to penicillin and other antimicrobial agents in metropolitan Toronto.

**DESIGN:** Consecutive pneumococcal isolates from different patients were obtained from two private community-based laboratories and from patients assessed in the emergency department of a tertiary-care teaching hospital in Toronto, Ontario between June and December 1993, and between March and October 1994. In vitro susceptibility testing was done by broth microdilution in accordance with National Committee for Clinical Laboratory Standards guidelines.

**RESULTS:** Twenty (7.3±3.1%) of 274 pneumococcal isolates were resistant to penicillin; six (30%) isolates had high-level resistance (minimal inhibitory concentration [MIC] 2.0 µg/mL or greater); and 14 isolates had intermediate resistance (MIC 0.1 to 1.0 µg/mL). Penicillin-resistant strains were also frequently resistant to tetracycline (55%), cotrimoxazole (50%), erythromycin (40%) and cefuroxime (35%). Resistant strains comprised several serotypes: 19F (six isolates), 9V (three), 23F (three), and one each of 6A, 6B, 14, and 19A; four isolates were nontypeable.

**CONCLUSIONS:** There has been a recent emergence of penicillin-resistant *S pneumoniae* in southern Ontario. National and regional surveillance is warranted to determine the extent of the problem elsewhere in Canada.

(Pour résumé, voir page 158)

**Key Words:** Antibiotic resistance, *Streptococcus pneumoniae*
Penicillin has long been considered to be the antibiotic of choice for the treatment of infections due to Streptococcus pneumoniae. In the past few years, though, there has been a worldwide increase in the prevalence of penicillin-resistant *S. pneumoniae* (1-3). Although a strain of pneumococcus with reduced susceptibility to penicillin was first reported in Canada 20 years ago (4), since then there have been only sporadic reports of invasive infections due to resistant organisms in this country (5-7). Three large surveys of pneumococcal susceptibility in Canada found rates of resistance to penicillin of 2.4%, 1.3% and 1.5% in Alberta (8), Quebec (9) and Ontario (10), respectively. Two recent cases of invasive infection (meningitis, bacteremic pneumonia) due to penicillin-resistant strains of *S. pneumoniae* seen at our hospital prompted us to conduct a pilot study to determine the prevalence of resistance of *S. pneumoniae* to penicillin and other antimicrobial agents in metropolitan Toronto. We describe here one of the cases and the results of the prevalence survey.

**CASE PRESENTATION**

A 45-year-old male with human immunodeficiency virus infection and central nervous system lymphoma was admitted to hospital in November 1993 with a two-day history of fever and dyspnea. His medications on admission included trimethoprim-sulfamethoxazole, fluconazole and prednisone. Physical examination revealed cellulitis over the anterior aspect of his neck, and a chest x-ray revealed left lower lobe consolidation. Blood and sputum cultures grew *S. pneumoniae* resistant to penicillin (minimal inhibitory concentration [MIC] 4 μg/mL). He was admitted to the intensive care unit with respiratory failure. He was treated with vancomycin for two weeks and was discharged from hospital. However, he was readmitted one month later with recurrent fever and bacteremia due to penicillin-resistant *S. pneumoniae*. He was retreated with vancomycin, but died several months later of causes unrelated to pneumococcal infection.
of which had high-level resistance and 14 with intermediate resistance (Table 1). Fourteen resistant strains were eye, ear or sputum isolates from pediatric out-patients and six strains (two from sputum and one each from blood, cerebrospinal fluid, bronchoalveolar washings and the eye) were from adults seen in the emergency department. Penicillin-susceptible strains were generally susceptible to the other antimicrobial agents tested. However, penicillin-resistant \textit{S. pneumoniae} were also frequently resistant to ceftazidime (55%), tetracycline (55%), trimethoprim-sulfamethoxazole (50%), erythromycin (40%), cefuroxime (35%) and ceftriaxone (25%) (Table 1). Isolates were uniformly susceptible to only vancomycin and imipenem.

The penicillin-resistant pneumococci were serotyped as follows: 19F (six isolates), 9V (three), 23F (three), and one each of 6A, 6B, 14, 19A; four were nontypeable. The PFGE results of a representative sample of penicillin-resistant isolates are shown in Figure 1. Different serotypes had clearly distinguishable PFGE patterns. However, whereas all three serotype 9V isolates had identical patterns and a nontypeable strain shared an identical pattern with a serotype 23F isolate, the other 23F serotypes had distinct profiles and each of the 19F serotype isolates had a unique pattern.

### DISCUSSION

The recent increase in the prevalence of penicillin-resistant \textit{S. pneumoniae} in the metropolitan Toronto region found in this survey is in marked contrast to results obtained in a 1988 study (10) of a similar community-based population when only eight of 551 (1.5%) penicillin-resistant strains were detected (P<0.0001). Furthermore, none of the previously identified pneumococcal isolates had demonstrated high-level penicillin resistance, whereas 30% of the resistant strains in this survey had high-level resistance.

The recent increase in prevalence is also reflected by notifications of invasive pneumococcal disease due to penicillin-resistant strains to the Ontario Pneumococcal Study Group (13) in 1993-94.

The results of serotyping and molecular typing by PFGE suggest that multiple clones of penicillin-resistant pneumococci are appearing simultaneously in the metropolitan Toronto region. Similar results have been suggested by a cross-Canada survey of penicillin-resistant isolates (14). Moreover, this preliminary experience with these typing methods suggests that for \textit{S. pneumoniae}, PFGE is more discriminatory than is serotyping; this observation would have to be confirmed by evaluating a larger number of isolates.

The emergence of penicillin-resistant \textit{S. pneumoniae} has major health care implications. Microbiology laboratories

### TABLE 1

Antimicrobial susceptibility of 274 isolates of \textit{Streptococcus pneumoniae}

<table>
<thead>
<tr>
<th>Antimicrobial agent</th>
<th>Penicillin-susceptible isolates (n=254)</th>
<th>Penicillin-resistant isolates (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MIC(_{90}) ((\mu)g/mL)*</td>
<td>% resistant</td>
</tr>
<tr>
<td>Penicillin</td>
<td>(\leq 0.06)</td>
<td>0</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>(\leq 0.06)</td>
<td>0</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>(\leq 0.06)</td>
<td>0</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>(\leq 0.06)</td>
<td>0</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>0.5</td>
<td>0.8</td>
</tr>
<tr>
<td>Imipenem</td>
<td>(\leq 0.06)</td>
<td>0</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>(\leq 0.5)</td>
<td>0.8</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>(\leq 0.5)</td>
<td>0</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>(\leq 2.0)</td>
<td>2.8</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>1.0</td>
<td>0.8</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>4.0</td>
<td>0.8</td>
</tr>
<tr>
<td>Trimethoprim-sulfamethoxazole</td>
<td>4.0</td>
<td>9.1</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>1.0</td>
<td>0</td>
</tr>
</tbody>
</table>

*MIC\(_{90}\): Minimal inhibitory concentration of antimicrobial agent required to inhibit growth of 90% of the isolates tested.
must be able to detect rapidly and accurately penicillin resistance in pneumococcal isolates. Although drug-resistant strains of pneumococci now appear to be much more prevalent in several parts of Canada, regional variations may exist. If the results of this survey are confirmed elsewhere in Canada, empirical antimicrobial treatment of a variety of infectious diseases (including pneumonia, bronchitis, otitis media, sinusitis and meningitis) will have to be modified. Treatment options may be limited because penicillin-resistant strains are also frequently resistant to other beta-lactam antibiotics (15,16). Moreover, alternative antimicrobial agents for the treatment of pneumococcal infections may not be as effective as penicillin would be for susceptible strains (17,18). Because invasive infections due to resistant strains are associated with considerable morbidity and mortality, greater use of pneumococcal vaccine should be promoted, particularly for those at high risk for severe pneumococcal infections (19). Continuous surveillance of *S. pneumoniae* antimicrobial susceptibility is required to determine the extent of resistance to penicillin and alternative agents, so that appropriate therapy and control measures may be instituted.

ACKNOWLEDGEMENTS: We thank Med-Chem and Flemingdon Medical Laboratories for providing pneumococcal isolates; the National Reference Centre for Streptococcus (Edmonton, Alberta) for serotyping isolates; and C McGowan-Schulze for secretarial services.

REFERENCES
