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PENICILLIN-RESISTANT *STREPTOCOCCUS PNEUMONIAE* IN ONTARIO, 1987-1995

Introduction

Streptococcus pneumoniae is a major cause of pneumonia, meningitis, septicemia, acute otitis media, and other serious infections[1], severely affecting infants, young children, and the elderly[2]. In the past, *S. pneumoniae* was uniformly susceptible to penicillin, which remained the drug of choice for serious infections. However, since the mid-1960s, resistance to penicillin, which was first reported in Australia[3], has been occurring with greater frequency in various parts of the world[4-7]. The percentage of penicillin-resistant *S. pneumoniae* (PRSP) isolates with resistance to other primary therapeutic agents such as trimethoprim/ sulfamethoxazole (TMP/SMX), erythromycin, tetracycline, and chloramphenicol as well as agents which are used for multi-drug resistant isolates, such as ceftriaxone and cefotaxime[5,8,9], is also increasing in various parts of the world. In Canada, an isolate with reduced susceptibility to penicillin was first reported in 1974[10], and a multi-resistant strain of *S. pneumoniae* was first reported in 1983[11]. A survey of the literature indicates that the prevalence of PRSP varies across Canada[12-14], and a recent report from Quebec shows that levels of resistance are increasing[15].

All isolates of *S. pneumoniae* submitted to the Central Public Health Laboratory, Toronto, have been tested for antimicrobial susceptibility since April 1987. This report describes the results of *S. pneumoniae* susceptibility to penicillin and other antimicrobial agents from April 1987 to April 1995.

Methods

Isolates: *S. pneumoniae* isolates were obtained from public-health laboratories, private community-based laboratories which provide services to physicians, nursing homes, clinics, and several hospitals across Ontario. Samples were collected from patients who were newborn to 88 years of age (median: 49 years), with clustering among patients < 2 years and > 60 years of age. Most isolates submitted for testing were resistant by oxacillin disk and therefore required further testing. A total of 1,144 non-duplicate isolates were tested.

Susceptibility testing: The following antimicrobial agents were tested by agar dilution at the following concentrations (mg/L): penicillin, 0.0037 to 2.0; erythromycin, 0.5 and 2.0; tetracycline, 2.0 and 4.0; chloramphenicol, 4.0; vancomycin, 1.0; TMP/SMX, 0.5/9.5 and 2.0/38.0; cefotaxime, 0.5 and 1.0; and ceftriaxone, 0.5 and 1.0. All isolates were screened for penicillin-resistance using the 1µg oxacillin disk according to National Committee for Clinical Laboratory Standards (NCCLS)[16]. The minimum inhibitory concentration (MIC) for penicillin-susceptible *S. pneumoniae* was MIC ≤ 0.06 mg/L; for isolates with intermediate resistance, MIC 0.12 to 1.0 mg/L, and for those with high resistance, MIC ≥ 2.0 mg/L.

Results

Of the total 1,144 *S. pneumoniae* isolates examined over the 8-year study, 493 (43.1%) demonstrated intermediate resistance to penicillin and 77 (6.7%) demonstrated high resistance. Table 1 shows the numbers and percentages of isolates with high and intermediate resistance by year. There was a greater fluctuation in the frequency of isolates with high resistance than in the frequency of isolates with intermediate resistance. The percentage of isolates with high resistance ranged from a high of 10% to a low of 1.3% from 1987 to 1990, and then rose steadily from 1.8% to 13.6% from 1991 to 1995. Isolates with intermediate resistance ranged from 35% to 53.6%.

Table 1
Numbers and percentages of *S. pneumoniae* isolates with reduced susceptibility to penicillin by year

Year	No. Tested	Resistance				Total	
		Intermediate* No. (%)		High** No. (%)		No. (%)	
1987[a]	28	15	(53.6)	1	(3.6)	16	(57.1)
1988	65	26	(40.0)	6	(9.2)	32	(49.2)
1989	60	21	(35.0)	6	(10.0)	27	(45.0)
1990	76	33	(43.4)	1	(1.3)	34	(44.7)
1991	111	42	(37.8)	2	(1.8)	44	(39.6)
1992	155	58	(37.4)	7	(4.5)	65	(41.9)
1993	208	98	(47.1)	10	(4.8)	108	(51.9)
1994	257	122	(47.5)	19	(7.4)	141	(54.9)
1995[b]	184	78	(42.4)	25	(13.6)	103	(56.0)

* MIC 0.12 to 1.0 mg/L
** MIC ≥ 2.0 mg/L)
a) April to December
b) January to April

Table 2 shows the numbers of *S. pneumoniae* isolates with reduced susceptibility to penicillin according to their sources. The majority were from sputa, 206 (36.1%); followed by isolates from eyes, 126 (22.1%); blood, 74 (13%); and ears, 53 (9.3%).

Table 3 shows the numbers and percentages of isolates with reduced susceptibility to penicillin that were resistant to other antimicrobial agents. Only one penicillin-susceptible isolate showing resistance to other antimicrobial agents was observed from 1987 to 1990. However, from 1991 to 1995, an overall 8.5% of penicillin-resistant isolates were resistant to one other tested agent and 25.2% were resistant to two or more. Resistance to TMP/SMX was common; 104 isolates were resistant to this agent. Of these, 96 (20.5%) had MICs ≥ 2.0/38.0 mg/L and 8 (1.7%) had MICs > 0.5/9.5, < 2.0/38.0 mg/L. Seventy-three isolates (15.8%) were resistant to erythromycin (MIC ≥ 2.0 mg/L), 70 (15.2%) to tetracycline (MIC ≥ 4.0 mg/L) and 21 (4.6%) to chloramphenicol (MIC ≥ 4.0 mg/L). Isolates susceptible to penicillin were generally susceptible to other antimicrobial agents. Only three showed resistance to other antimicrobials; one was resistant to erythromycin and TMP/SMX, another to erythromycin and tetracycline, and the other to erythromycin, tetracycline and TMP/SMX (MICs > 2.0 mg/L, > 4.0 mg/L, and ≥ 2.0/38.0 mg/L for erythromycin, tetracycline and TMP/SMX, respectively).

Table 2
Numbers of *S. pneumoniae* isolates with intermediate and high resistance to penicillin according to source of specimen, 1987-1995

Source of Specimen	Resistance		Total No.
	Intermediate* No.	High** No.	
Ear	43	10	53
Nose	24	3	27
Nasopharynx	1	1	2
Throat	11	0	11
Eye	119	7	126
Blood	66	8	74
CSF	4	0	4
Sputa	171	35	206
Endotracheal aspirate	6	0	6
Bronchial wash	22	2	24
Bronchial brush	0	1	1
Auger suction	12	2	14
Pleural fluid	1	0	1
Others	10	3	13
Unknown	7	1	8

* MIC 0.12 to 1.0 mg/L
** MIC ≥ 2.0 mg/L

Table 3
Numbers and percentages of *S. pneumoniae* isolates with reduced susceptibility to penicillin, associated with resistance to other antimicrobial agents, 1987-1995

Year	No. (I* + H**)	(I* or H**) + resistance to one other antimicrobial agent resistance No. (%)		(I* or H**) + resistance to two or more antimicrobial agents No. (%)	
1987	16	0	(0)	0	(0)[a]
1988	32	0	(0)	0	(0)
1989	27	0	(0)	0	(0)
1990	34	0	(0)	0	(0)
1991	44	0	(0)	5	(11.4)
1992	65	0	(0)	2	(3.1)
1993	108	1	(0.09)	8	(7.4)
1994	141	13	(9.2)	59	(41.5)[b]
1995	103	25	(24.3)	42	(40.8)[c]

* I = intermediate resistance (MIC 0.12 to 1.0 mg/L)
** H = high resistance (MIC ≥ 2.0 mg/L)
a) One isolate was resistant to erythromycin and TMP/SMX (MICs > 2.0 and > 2.0/38.0 mg/L, respectively), but susceptible to penicillin (MIC < 0.06 mg/L).
b) One isolate was resistant to erythromycin and tetracycline (MICs > 2.0 and > 4.0 mg/L, respectively), but susceptible to penicillin (MIC < 0.06 mg/L).
c) One isolate was resistant to erythromycin, tetracycline and trimethoprim/sulfamethoxazole (MICs > 2.0, > 4.0 and > 2.0/38.0 mg/L, respectively), but susceptible to penicillin (MIC < 0.06 mg/L).

From April 1994 to April 1995, 207 isolates with reduced susceptibility to penicillin were tested for resistance to ceftriaxone and cefotaxime. Of these, 10 (4.8%) showed high resistance (MIC ≥ 2.0 mg/L) to cefotaxime or to both cefotaxime and ceftriaxone; 56 (27.1%) showed intermediate resistance (MIC 1.0 mg/L) to cefotaxime or ceftriaxone, or to both cefotaxime and ceftriaxone (Table 4). Of the isolates with high resistance to cefotaxime and ceftriaxone, six were from sputa, one from bronchial washings, one from blood, one from eyes, and one from the lower abdomen. Isolates with intermediate resistance to the cephalosporins were from various sources; sputa (25), ear (11), eye (9), and blood (6). None of the penicillin-susceptible isolates were resistant to the cephalosporins. The most common resistances were intermediate ones to ceftriaxone and cefotaxime as well as to TMP/SMX (11 isolates); to ceftriaxone and cefotaxime as well as to TMP/SMX and erythromycin (6 isolates); to ceftriaxone and cefotaxime (6 isolates); and to ceftriaxone and cefotaxime as well as to TMP/SMX, tetracycline, and chloramphenicol (5 isolates). All isolates were susceptible to vancomycin.

Discussion

S. pneumoniae remains a major causative agent of serious human disease, particularly of community-acquired pneumonia. A number of reports have shown that the incidence of disease caused by *S. pneumoniae* is highest in infants < 2 years of age and in adults > 60 years of age[17]. A similar age distribution was observed in this study. Penicillin is considered the drug of choice for pneumococcal infections[18]; in recent years, however, isolates of *S. pneumoniae* with decreased susceptibility to penicillin have been occurring with increasing frequency[4,5,6]. The prevalence of isolates of *S. pneumoniae* with intermediate or high resistance to penicillin varies worldwide. Some of the highest incidences of these isolates have been reported from Spain (51%)[6], Hungary (57.8%)[19], South Africa (62.2%)[5] and Korea (70%)[20]. Reports in Canada have ranged from 1.5% in Southern Ontario[13], to 1.3% in Quebec[14], and 2.4% in Western Canada[12].

In the present study, the prevalence of isolates with reduced susceptibility to penicillin was higher than that previously reported in Canada. Moreover, between 1991 and 1995, there was an annual increase in the percentage of such isolates. The increase of isolates with high resistance was more significant than the increase of ones with intermediate resistance (Table 1). Between 1987 and 1990, there was a wide variation in the percentage of isolates which showed a high resistance to penicillin; the decrease from 10% in 1989 to 1.3% in 1990 is of note. The reason for this change is unknown. The authors suspect that mostly resistant isolates of *S. pneumoniae* were referred to the Central Public Health Laboratory from 1988 to 1989 for confirmation while isolates were submitted in later years regardless of their susceptibility pattern. Also, between 1987 and 1990, the majority of isolates were from hospitals across Ontario (58%, 65%, 66%, and 70%, respectively), compared to a more even distribution among hospitals and community isolates in later years.

The first multi-resistant *S. pneumoniae* reported in Canada was resistant to penicillin and chloramphenicol[11]. In this study, only a small percentage of isolates showed resistance to chloramphenicol. Isolates with reduced susceptibility to penicillin were associated mainly with resistance to TMP/SMX followed by resistance to erythromycin and tetracycline. It is noteworthy that 18 of 21 (85.7%) of chloramphenicol-resistant isolates were associated with resistance to the cephalosporins (Table 4).

Table 4
Association of *S. pneumoniae* isolates with reduced susceptibility to penicillin with resistance to cefotaxime, ceftriaxone and other antimicrobial agents

Resistance pattern[a]	No. of isolates with patterns
Tax, TMP/SMX	1
Tax, TMP/SMX, Tc	1
Tax, Tri	2
Tax, Tri, TMP/SMX	3
Tax, Tri, (TMP/SMX)[b]	1
Tax, Tri, Tc, Cm	1
Tax, (Tri)1TMP/SMX, Tc, Cm, Em	1
Tax[b]	3
Tax[b], TMP/SMX	2
Tax[b], TMP/SMX, Tc, Cm	3
Tax[b], TMP/SMX, Tc, Cm, Em	1
Tax[b], TMP/SMX	1
(Tax, Tri)[b]	6
(Tax, Tri)[b], TMP/SMX	11
(Tax, Tri)[b], TMP/SMX, Tc	1
(Tax, Tri)[b], TMP/SMX, Tc, Cm	5
(Tax, Tri)[b], TMP/SMX, Tc, Em	3
(Tax, Tri)[b], TMP/SMX[b], Tc, Em	3
(Tax, Tri)[b], TMP/SMX, Cm, Em	2
(Tax, Tri)[b], TMP/SMX, Cm	2
(Tax, Tri)[b], TMP/SMX, Cm, Tc, Em	1
(Tax, Tri)[b], TMP/SMX, Em	6
(Tax, Tri)[b], Tc, Em[b]	1
(Tax, Tri)[b], Tc, Em	1
(Tax, Tri)[b], Tc, Cm	1
(Tax, Tri)[b], Tc, Cm, Em	1
(Tax, Tri)[b], Em	2

[a] Tax, cefotaxime; Tri, ceftriaxone; Em, erythromycin; Cm, chloramphenicol; Tc, tetracycline;TMP/SMX, trimethoprim/sulfamethoxazole.
[b] Intermediate resistance

In 1988, a 5-month study of isolates from community outpatients across Ontario also found resistance to TMP/SMX to be the most common[13]. A study of isolates from the metropolitan Toronto area reported that resistance to tetracycline was more commonly found with penicillin-resistance in S. pneumoniae[21]. Chloramphenicol-resistant S. pneumoniae have been reported in large numbers in Quebec[15], and are associated mainly with isolates with high resistance to penicillin. In this study, penicillin-susceptible S. pneumoniae isolates were generally susceptible to all other antimicrobial agents tested. Only three penicillin-susceptible isolates were also resistant to TMP/SMX, erythromycin, and tetracycline.

S. pneumoniae isolates resistant to these broad-spectrum cephalosporins are of particular concern since these agents are recommended for serious infections, such as meningitis and septicemia, especially when such isolates show intermediate or high resistance to penicillin. Resistance to cefotaxime and ceftriaxone was present in four isolates with high resistance to penicillin, and in six isolates with intermediate resistance. Of the 56 isolates with intermediate resistance to the cephalosporins (MIC 1.0 mg/L), 31 were associated with high resistance to penicillin and 25 with intermediate resistance to penicillin. A number of studies have indicated that isolates resistant to cefotaxine or ceftriaxone have been seen in patients who have failed treatment(22,23). Clinical information was unavailable for this study.

In summary, data show an increase in the numbers of S. pneumoniae isolates, submitted to Central Public Health Laboratory, which are highly resistant to penicillin. Many of these also showed multi-resistance to other primary therapeutic agents and third generation cephalosporins. These results emphasize the importance of continued monitoring of the patterns of susceptibility among *S. pneumoniae*.

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Editorial Comment

The above study reports the frequencies of intermediate- and high-level resistance to penicillin to be 43% and 7%, respectively, among 1,144 pneumococcal isolates submitted to an urban public-health laboratory over an 8-year period. It contributes to the growing literature describing antimicrobial-resistant *S. pneumoniae* in Canada. All such studies should be considered carefully because they may differ in important elements, including clinical source of specimen (sterile vs. non-sterile site), age of subjects sampled, and type of reporting laboratories (hospital vs. public-health). The increased rates of resistance to penicillin reported in this study compared with others likely reflects some of these differences. A recent Canada-wide, hospital-based survey of pneumococcal infection in children reported that 1.6% and 0.4% of invasive pneumococcal isolates showed intermediate- and high-level resistance, respectively. Continued laboratory and population-based national surveillance for antimicrobial-resistant *S. pneumoniae* is essential in monitoring this evolving problem.

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