# Invasive *Streptococcus pneumoniae* infections: serotype distribution and antimicrobial resistance in Canada, 1992–1995

*Evidence*

*Études*

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## Abstract

**Objective:** To report current information about invasive pneumococcal infections, capsular types and antimicrobial resistance in Canada.

**Design:** Retrospective analysis.

**Setting:** Canada.

**Patients:** A total of 976 patients from whom *Streptococcus pneumoniae* was isolated from blood or cerebrospinal fluid between Jan. 1, 1992, and Dec. 31, 1995.

**Outcome measures:** Capsular type and antimicrobial susceptibility.

**Results:** Twenty types accounted for 90.8% of the isolates from patients over 5 years of age; all but type 15A are covered by the currently available 23-valent vaccine. Nine types accounted for 92% of the isolates recovered from children 5 years and less. Reduced susceptibility to penicillin was found in 7.8% of the collection and was associated with types 6B, 9V and 19A. Full resistance to penicillin was observed most frequently during 1995 and was associated with type 9V. Rates of reduced susceptibility over one 12-month period were 19.5% for trimethoprim–sulfamethoxazole and 4.5% or less for each of cefotaxime, ceftriaxone, chloramphenicol, erythromycin, ofloxacin and tetracycline.

**Conclusions:** Over 90% of invasive pneumococcal infections are covered by the currently available vaccines (for people over 2 years of age) and the pneumococcal protein-polysaccharide conjugate vaccines under development for young children. The high frequency of antimicrobial resistance observed requires more complete investigation and confirmation; however, taken from a global perspective, it supports the need to develop better control strategies, including greater use of new and existing vaccines.

## Résumé

**Objectif :** Présenter l'information courante sur les infections à pneumocoques envahissantes, les types capsulaires et la résistance aux antimicrobiens au Canada.

**Conception :** Analyse rétrospective.

**Contexte :** Canada.

**Patients :** Au total, 976 patients chez lesquels on a isolé le *Streptococcus pneumoniae* dans des spécimens de sang ou de liquide céphalo-rachidien entre le 1er janvier 1992 et le 31 décembre 1995.

**Mesures de résultats :** Type capsulaire et sensibilité aux antimicrobiens.

**Résultats :** Vingt types ont représenté 90,8 % des isolats provenant de patients âgés de plus de cinq ans. Le vaccin à 23 valences actuellement disponible couvre tous les types sauf le type 15A. Neuf types ont représenté 92 % des isolats prélevés chez des enfants âgés de cinq ans et moins. On a constaté une sensibilité réduite à la pénicilline dans 7,8 % des échantillons prélevés, réduction qu'on a associée aux types 6B, 9V et 19A. On a observé une résistance complète à la pénicilline le plus souvent en 1995 et l'on a associé cette résistance au type 9V. Les taux de réduction de la sensibilité au cours d'une période de 12 mois ont été de 19,5 % dans le cas du triméthoprime–sulfaméthoxazole et de 4,5 % au

moins dans celui du céfotaxime, de la ceftriaxone, du chloramphénicol, de l'érythromycine, de l'ofloxacine et de la tétracycline.

**Conclusions :** Les vaccins actuellement disponibles (pour les personnes qui ont plus de deux ans) et les vaccins antipneumococciques conjugués aux protéines et aux polysaccharides qu'on est en train de mettre au point pour les jeunes enfants couvrent plus de 90 % des infections envahissantes à pneumocoques. Il faut étudier plus à fond et confirmer la fréquence élevée de résistance aux antimicrobiens qu'on a observée. Dans une optique globale, toutefois, cette résistance démontre qu'il faut élaborer de meilleures stratégies de contrôle et notamment utiliser davantage des vaccins nouveaux et existants.

*Streptococcus pneumoniae* is the leading cause of community-acquired bacterial pneumonia and a major cause of bacteremia, meningitis and otitis media.[1–3] Elderly people and people with underlying disease are particularly vulnerable, and in the very young this organism is now the most common cause of invasive bacterial infection. In one study in the United States, the incidence of pneumococcal bacteremia was 52.8 per 100 000 among people more than 65 years old and 162 per 100 000 among children less than 2 years old; the rate of death among elderly people was 44%.[4]

The increasing prevalence of antibiotic resistance among pneumococci is well documented[5–11] and is occurring in North America.[3,12–15] In 1992 the rate of reduced susceptibility to penicillin in Canada was thought to be less than 5%.[9] Since 1994, reports from eastern Canada have identified rates of 7.3% to 8.1%,[16,17] and one recent national survey reported a rate of 11.7%.[18]

There are 90 known pneumococcal capsular types,[19] and those associated with disease vary temporally and geographically.[2,20–22] Our ability to estimate the impact of currently available 23-valent vaccines and protein-polysaccharide conjugate vaccines being developed for young children depends on our knowledge of the capsular types causing disease in specific age groups and of the types associated with increasing antibiotic resistance. We report data retrieved from 1992 through 1995 on capsular types of *S. pneumoniae* recovered from Canadian children and adults and examine current trends in antibiotic resistance for this organism and the implications.

## Methods

The National Centre for Streptococcus (NCS), operated in partnership with Health Canada's Laboratory Centre for Disease Control, Ottawa, provides pneumococcal serotyping services for invasive isolates submitted from across Canada. Participation in this passive surveillance system is solicited through provincial public health laboratories and is limited by the level of interest and the resources available in each province.

Our study sample included all isolates of *S. pneumoniae* sent to the NCS for serotyping between Jan. 1, 1992, and Dec. 31, 1995, that were recovered from blood or cerebrospinal fluid and were not part of specified study collections. Demographic information was reviewed to eliminate duplicate patient isolates. Identification was confirmed by optochin susceptibility and bile solubility.[23]

Capsular typing (Danish nomenclature) was performed by means of the quellung reaction[23] using pool, group, type and factor sera from Statens Seruminstitut, Copenhagen.

All isolates were screened for penicillin susceptibility using a 1-μg oxacillin disk.[24] Those with zones of 19 mm or less were tested to determine the minimum inhibitory concentration (MIC) for penicillin G. All blood isolates received from Apr. 1, 1993, to Mar. 31, 1994, were tested by means of broth microdilution, according to the National Committee for Clinical Laboratory Standards,[25] against penicillin, cefotaxime, ceftriaxone, chloramphenicol, erythromycin, ofloxacin, tetracycline, trimethoprim–sulfamethoxazole and vancomycin. We defined reduced susceptibility as including intermediate and resistant categories, and multiple resistance as including reduced susceptibility to 3 or more classes of antibiotics.

We used the Mantel–Haenszel $\chi^2$ test and, where the cell frequency was less than 5, the Fisher exact (2-tailed) test to compare differences in proportions. The $\chi^2$ test was used for linear trend (EpiInfo, version 6.03; US Centers for Disease Control and Prevention, Atlanta) to assess differences in serotype distribution and antibiotic resistance patterns over time.

## Results

Isolates from 976 patients were serotyped; 894 (91.6%) of the patients had isolates from blood, 58 (5.9%) from cerebrospinal fluid and the remaining 24 (2.5%) from both sites; the paired isolates belonged to the same type. A total of 303 patients were 5 years of age or younger, and 643 were over 5 years; age was unspecified for 30 patients.

Pneumococcal isolates were received from all provinces and territories except Prince Edward Island (Table 1); the largest proportion (48%) was from Alberta. Because the

number of isolates submitted from Alberta was about 9-fold greater per population than the number in the rest of Canada, the distribution of serotypes from Alberta was compared with that of serotypes from the other provinces and the territories. The differences in serotype distribution between the 2 geographic areas were not statistically significant except for type 8 ($p < 0.001$), submitted only from Alberta. The following analysis is for all isolates.

Expected vaccine coverage for this collection is presented in Table 2. Among the most common 20 types, only type 15A is not covered by the currently available 23-valent vaccine. In total, 896 (91.8%) of the isolates belonged to or could possibly cross-react[20] with antibody to a capsular type included in this vaccine. Vaccine coverage may be expected for 89.7% (577/643) of the isolates recovered from people over 5 years of age. For children 5 years or younger, 9 types accounted for 92.1% of the collection, all of which are covered by the 23-valent vaccine; the top 7 types are also included in a 7-valent conjugate vaccine undergoing clinical trial.[26]

The 9 most common capsular types for the 2 age groups are compared in Fig. 1. Although type 14 was a common cause of invasive infection in all ages, the proportion of disease due to this type was greater among children aged 5 years or less than among people in the other age group ($p < 0.001$). Types 6B, 19F and 18C were associated with invasive disease in the younger age group, and types 22F, 1 and 3 were associated with invasive disease in the older age group ($p < 0.01$).

Of the 976 isolates 80 (8.2%) produced oxacillin zones of 19 mm or less. Four (5%) of the 80 were susceptible to penicillin. Table 2 shows the rate of reduced susceptibility to penicillin as it relates to potential vaccine coverage. Of the 76 isolates with reduced susceptibility 68 (89.5%) belonged to 6 serotypes. Overall, reduced susceptibility to penicillin was associated with types 9V, 19A and 6B ($p < 0.001$). Type 9V isolates were more likely to be fully resistant to penicillin ($p < 0.001$). There was a significant trend toward full resistance between 1992 and 1995 ($\chi^2$ for trend = 15.6; $p < 0.001$) but not for the overall change in reduced susceptibility over the 4-year period. There was no difference in the frequency of reduced susceptibility to penicillin between isolates from Alberta and those from the rest of Canada.

From April 1993 through March 1994, 154 isolates from blood were evaluated for susceptibility to 9 antibiotics. Of these, 40 (26.0%) were found to have reduced susceptibility to one or more of the drugs. The proportion of isolates with reduced susceptibility were 9.7% to penicillin (including 1.3% with an MIC of 2.0 μg/mL or higher), 3.2% to cefotaxime, 3.9% to ceftriaxone, 2.0% to chloramphenicol, 4.5% to erythromycin, 2.6% to ofloxacin, 4.5% to tetracycline and 19.5% to trimethoprim–sulfamethoxazole. All 154 isolates were susceptible to vancomycin. Of 14 isolates with reduced susceptibility to penicillin, 10 had intermediate or full resistance to trimethoprim–sulfamethoxazole. Only 10 of 30 isolates with reduced susceptibility to trimethoprim–sulfamethoxazole had intermediate or full resistance to penicillin.

Full resistance (MIC 2.0 μg/mL or higher) to third-generation cephalosporins was detected in 2 strains with intermediate resistance to penicillin (MIC 0.5 and 1.0 μg/mL respectively). For the remaining 152 isolates, the MICs to the extended-spectrum cephalosporins were less than or equal to the MICs to penicillin.

Six (3.9%) of the 154 isolates were classified as having multiple resistance, exhibiting 5 resistance patterns. These

**Table 1: Distribution of submitted isolates in Canada**

| Province/territory | Total no. of isolates | No. of isolates per 100 000 annually* |
|---|---|---|
| British Columbia | 66 | 0.44 |
| Alberta | 471 | 4.28 |
| Saskatchewan | 18 | 0.44 |
| Manitoba | 30 | 0.66 |
| Ontario | 282 | 0.64 |
| Quebec | 51 | 0.17 |
| New Brunswick | 13 | 0.43 |
| Nova Scotia | 9 | 0.24 |
| Prince Edward Island | 0 | – |
| Newfoundland | 1 | 0.04 |
| Yukon and Northwest Territories | 35 | 9.72 |
| Total | 976 | 0.82 |

*Based on 1995 population projections from 1991 census.

**Table 2: Vaccine coverage of pneumococcal serotypes and relation to penicillin susceptibility**

| | No. (and %) of isolates by age | | No. (and %) of isolates by penicillin susceptibility | | |
|---|---|---|---|---|---|
| Serotype status | All ages | ≤ 5 yr | Susceptible | Intermediate | Resistant |
| Covered* by 23-valent vaccine | 896 (91.8) | 289 (95.4) | 827 (91.9) | 42 (85.7) | 27 (100) |
| Covered* by 7-valent vaccine[26] | 638 (65.4) | 273 (90.1) | 582 (64.7) | 29 (59.2) | 27 (100) |
| Not covered by either vaccine | 80 (8.2) | 14 (4.6) | 73 (8.1) | 7 (14.3) | 0 (0) |
| Total | 976 | 303 | 900 | 49 | 27 |

*Includes cross-protection expected for serotype 6A.[20]

isolates expressed reduced susceptibility to penicillin (3), chloramphenicol (3), erythromycin (4), tetracycline (5) and trimethoprim–sulfamethoxazole (6). Five were type 6B and one was nontypable.

## Discussion

Surveillance for *S. pneumoniae* infections has become increasingly important because of the emergence of antimicrobial-resistant strains and because of the need for current information on capsular types causing disease in young children, given the availability of new pneumococcal protein-polysaccharide conjugate vaccines in the near future. Pneumococcal infections are not notifiable in Canada, and current laboratory-based surveillance depends on the voluntary submission of isolates. Awareness and commitment to surveillance are factors that influence isolate referral, but they should not affect capsular type distribution because this information is unknown to the submitting agency. Geographic proximity probably contributed to the more complete sampling of strains from Alberta, and this may have affected the distribution of types observed. However, the similarity of capsular type distribution between Alberta and the rest of Canada suggests that one can still draw valid conclusions for the country as a whole from this collection.

Resistance to penicillin is a factor that may have influenced referral of an isolate, resulting in the greater likelihood of a resistant strain being sent to the NCS. Overall, 9.1% of the isolates from Alberta showed some level of penicillin resistance, as compared with 6.5% from the rest of Canada. The lack of a significant difference in the proportion of isolates having reduced susceptibility to penicillin between Alberta and the rest of Canada suggests that strains being sent from the rest of Canada were not more likely to be resistant. Alternatively, the predominant factor influencing isolate referral is the interest of submitting laboratories in this surveillance activity; referral of an isolate based only on the results of antimicrobial susceptibility testing is of less importance.

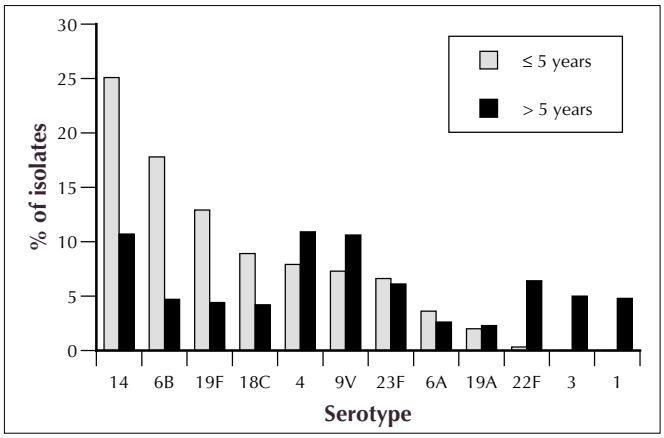


**Fig. 1: Age distribution of the most common serotypes of *Streptococcus pneumoniae* in Canada isolated from 1992 to 1995.**

Although we were unable to identify precisely the true level of antimicrobial resistance among *S. pneumoniae* isolates in Canada because of the passive surveillance, the overall trends of increasing full resistance to penicillin[3,31] as well as the emergence of resistance within specific capsular types[6–9] are consistent with trends observed in the United States and other countries. We believe that our results represent important and valid trends for Canada.

All but 3 of the 76 isolates with reduced susceptibility to penicillin belonged to serogroups 6, 9, 14, 19 and 23, groups associated with penicillin resistance worldwide.[3,6–8,11,12,15] Type 9V was most commonly associated with full penicillin resistance in our collection, although the majority of resistant strains previously reported from Quebec belonged to serogroup 23.[13,27] This difference may have been due to separate clonal invasions of resistant organisms acquired elsewhere. A resistant type 9V strain originated in Spain[11] and is spreading in France,[28] and the world-wide spread of a Spanish type 23F clone is well documented.[28,29] Further analysis of these type 9V strains is currently under way.

Reduced susceptibility to trimethoprim–sulfamethoxazole was uncommon in North America before 1990,[3,12,30] but it has increased in recent years, to 18%–26% in the US.[15,31] The high proportion of isolates with reduced susceptibility to this drug in our study is consistent with a recent Canadian survey reporting a resistance rate of 18.5%.[18] It is important for clinicians to be aware that resistance to trimethoprim–sulfamethoxazole commonly occurs in penicillin-susceptible strains.[3,18]

Increasing antibiotic resistance strongly supports the need to consider vaccination as a means to prevent pneumococcal infections. The currently available 23-valent vaccine has an efficacy estimated to be 57%–58% for preventing bacteremia,[32,33] and it protects against almost all the capsular types for which antibiotic resistance has been reported. Adult vaccination against pneumococcal disease has been underutilized in North America.[34] The Ontario pneumococcal vaccine program for adults 65 years of age or older[35] is, we hope, the beginning of more widespread use in Canada.

Ongoing surveillance programs for invasive pneumococcal disease can be used to monitor the appropriateness of existing vaccine formulations and changes in antimicrobial susceptibility. Information about the latter will be important for programs being developed to improve antibiotic use by clinicians.

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## References


1. Shapiro ED, Austrian R. Serotypes responsible for invasive *Streptococcus pneumoniae* infections among children in Connecticut. *J Infect Dis* 1994;169:212-4.
2. Butler JC, Breiman RF, Lipman HB, Hofmann J, Facklam RR. Serotype distribution of *Streptococcus pneumoniae* infections among preschool children in the United States, 1978–1994: implications for development of a conjugate vaccine. *J Infect Dis* 1995;171:885-9.
3. Breiman RF, Butler JC, Tenover FC, Elliot JA, Facklam RR. Emergence of drug-resistant pneumococcal infections in the United States. *JAMA* 1994; 271:1831-5.
4. Breiman RF, Spika JS, Navarro VJ, Darden PM, Darby CP. Pneumococcal bacteremia in Charleston County, South Carolina a decade later. *Arch Intern Med* 1990;150:1401-5.
5. Chesney PJ. The escalating problem of antimicrobial resistance in *Streptococcus pneumoniae*. *Am J Dis Child* 1992;146:912-6.
6. Klugman KP, Koornhof HJ. Drug resistance patterns and serogroups or serotype of pneumococcal isolates from cerebrospinal fluid or blood, 1979–1986. *J Infect Dis* 1988;158:956-64.
7. Friedland IR, Klugman KP. Antibiotic-resistant pneumococcal disease in South African children. *Am J Dis Child* 1992;146:920-3.
8. George RC, Ball LC, Cooper PG. Antibiotic-resistant pneumococci in the United Kingdom. *Commun Dis Rep CDR Rev* 1992;2:R37-43.
9. Appelbaum PC. Antimicrobial resistance in *Streptococcus pneumoniae*: an overview. *Clin Infect Dis* 1992;15:77-83.
10. Leggiadro RJ. Penicillin- and cephalosporin-resistant *Streptococcus pneumoniae*: an emerging microbial threat. *Pediatrics* 1994;93:500-3.
11. Fenoll A, Bourgon CM, Munoz R, Vicioso D, Casal J. Serotype distribution and antimicrobial resistance of *Streptococcus pneumoniae* isolates causing systemic infections in Spain, 1979–1989. *Rev Infect Dis* 1991;13:56-60.
12. Spika JS, Facklam RR, Plikaytis BD, Oxtoby MJ. Antimicrobial resistance of *Streptococcus pneumoniae* in the United States, 1979–1987. *J Infect Dis* 1991; 163:1273-8.
13. *Streptococcus pneumoniae* with reduced susceptibility to penicillin G — Quebec. *Can Dis Wkly Rep* 1994;20:69-73.
14. Friedland IR, Shelton S, Paris M, Rinderknecht S, Ehrett S, Krisher K, et al. Dilemmas in diagnosis and management of cephalosporin-resistant *Streptococcus pneumoniae* meningitis. *Pediatr Infect Dis J* 1993;12:196-200.
15. Hofmann J, Cetron MS, Farley MM, Baughman WS, Facklam RR, Elliot JA, et al. The prevalence of drug-resistant *Streptococcus pneumoniae* in Atlanta. *N Engl J Med* 1995;333:481-6.
16. Loo VG, Lavellee J, McAlear D, Robson HG. The in-vitro susceptibilities of 326 *Streptococcus pneumoniae* isolates to nine antimicrobial agents including penicillin and newer quinolones. *J Antimicrob Chemother* 1994;33:641-5.
17. Simor AE, Rachlis A, Louie L, Goodfellow J, Louie M. Emergence of penicillin-resistant *Streptococcus pneumoniae* in southern Ontario, 1993–94. *Can J Infect Dis* 1995;6:157-60.
18. Simor AE, Louie M, Canadian Bacterial Surveillance Network, Low DE. Canadian national survey of prevalence of antimicrobial resistance among clinical isolates of *Streptococcus pneumoniae*. *Antimicrob Agents Chemother* 1996;40:2190-3.
19. Henrichsen J. Six newly recognized types of *Streptococcus pneumoniae*. *J Clin Microbiol* 1995;33:2759-62.
20. Robbins JB, Austrian R, Lee CJ, Rastogi SC, Schiffman G, Henrichsen J, et al. Considerations for formulating the second-generation pneumococcal capsular polysaccharide vaccine with emphasis on the cross-reactive types within groups. *J Infect Dis* 1983;148:1136-59.
21. Neilsen SV, Henrichsen J. Capsular types of *Streptococcus pneumoniae* isolated from blood and CSF during 1982–1987. *Clin Infect Dis* 1992;15:794-8.
22. Sniadack DH, Schwartz B, Lipman H, Bogaerts J, Butler JC, Dagan R, et al. Potential interventions for the prevention of childhood pneumonia: geographic and temporal differences in serotype and serogroup distribution of sterile site pneumococcal isolates from children — implications for vaccine strategies. *Pediatr Infect Dis J* 1995;14:503-10.
23. Facklam RR, Washington JA II. *Streptococcus* and related catalase-negative gram-positive cocci. In: Balows A, Hausler WJ Jr, Herrmann KL, Isenberg HD, Shadomy HJ, editors. *Manual of clinical microbiology*. 5th ed. Washington: American Society for Microbiology; 1991. p. 238-57.
24. National Committee for Clinical Laboratory Standards. *Performance standards for antimicrobial disk susceptibility tests*. 5th ed. Approved standard. Document M2-A5. Villanova (PA): The Committee; 1993.
25. National Committee for Clinical Laboratory Standards. *Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically*. 3rd ed. Approved standard. Document M7-A3. Villanova (PA): The Committee; 1993.
26. Anderson EL, Kennedy DJ, Geldmacher KM, Donnelly J, Mendelman PM. Immunogenicity of heptavalent pneumococcal conjugate vaccine in infants. *J Pediatr* 1996;128:649-53.
27. Jette LP, Ringuette L, Dascal A, Lapointe J. Pneumococcal resistance to antimicrobial agents in the province of Quebec, Canada. *J Clin Microbiol* 1994;32:2572-5.
28. Lefevre JC, Bertrand MA, Faucon G. Molecular analysis by pulsed-field gel electrophoresis of penicillin-resistant *Streptococcus pneumoniae* from Toulouse, France. *Eur J Clin Microbiol Infect Dis* 1996;14:491-7.
29. Munoz R, Coffey TJ, Daniels M, Dowson CG, Laible G, Casal J, et al. Intercontinental spread of a multiresistant clone of serotype 23F *Streptococcus pneumoniae*. *J Infect Dis* 1991;164:302-6.
30. Survey of antimicrobial susceptibility of community isolates of *Streptococcus pneumoniae* in Ontario. *Can Dis Wkly Rep* 1989;15:131-3.
31. 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.
32. Butler JC, Breiman RF, Campbell JF, Lipman HB, Broome CV, Facklam RR. Pneumococcal polysaccharide vaccine efficacy. *JAMA* 1993;270:1826-31.
33. Increasing pneumococcal vaccination rates among patients of a national health-care alliance — United States, 1993. *MMWR* 1995;44:741-4.
34. Fedson DS. Influenza and pneumococcal vaccination in Canada and the United States, 1980–1993: What can the two countries learn from each other? *Clin Infect Dis* 1995;20:1371-6.
35. Ross I. MDs short of pneumonia vaccine. *Globe and Mail* [Toronto] 1996 Nov 4; Sect A:3.


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