

# Invasive Pneumococcal Infections in Canadian Children, 1998-2003

## Implications for New Vaccination Programs

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### ABSTRACT

**Background:** We conducted active surveillance for invasive pneumococcal disease to assess the serotype and antibiotic resistance patterns in Canada prior to universal infant immunization programs, in most provinces.

**Methods:** Active surveillance was conducted by the 12 centres of the Canadian Paediatric Society's Immunization Monitoring Program, Active (IMPACT). This report includes children 16 years of age and younger with *S. pneumoniae* isolated from a normally sterile site, in 1998-2003.

**Results:** During six years of surveillance, 1,868 eligible cases were reported. The 7-valent pneumococcal conjugate vaccine (PCV7) matched 79% of isolates, including 84% from 6-23 month olds and 80% from 2-5 year olds. The proportion of isolates matched by PCV7 significantly decreased over the surveillance period from 81% in 1998 to 73% in 2003 ( $p=0.005$ ). The 23-valent polysaccharide vaccine (PPS) matched 90% of isolates from children 2 years or older.

Penicillin non-susceptibility rate was stable at 16% of isolates. Cefotaxime/ceftriaxone resistance rate was 5% and limited to penicillin-resistant isolates. Serotypes found in PCV7 accounted for 89% of penicillin-resistant isolates (100% including cross-reacting types 6A and 19A).

**Conclusion:** PCV7 matched three quarters of the isolates from young children as immunization programs began; therefore some program failures are inevitable. Children  $\geq 5$  years with predisposing conditions need the broader protection of 23-valent PPS vaccine and special attention from providers to ensure receipt. The rate of penicillin resistance remained steady over the last six years. The majority of isolates non-susceptible to penicillin are found in PCV7.

**MeSH terms:** Pneumococcal infections; drug resistance; pneumococcal vaccines

*La traduction du résumé se trouve à la fin de l'article.*

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*Streptococcus pneumoniae* is the primary cause of invasive bacterial infections among children.<sup>1</sup> Over 90 pneumococcal serotypes have been identified. The dominant types differ by continent and slowly change over time.<sup>2-5</sup> For example, the four most common serotypes ranked in order of occurrence in North American children are 14, 6, 19 and 18, while in South America serotypes 14, 6, 1 and 5 and in Asia serotypes 1, 19, 6 and 5 occur most frequently.<sup>5</sup> Currently, the 7 serotypes most commonly identified in invasive disease in North America have been included in a 7-valent pneumococcal conjugate vaccine (PCV7); however, these 7-types were not always the most prevalent in North America.<sup>5,6</sup> In the 1930s, serotypes 1, 2, 3, 5 and 7 occurred frequently until about the mid-1950s when the serotypes found in PCV7 started increasing.<sup>6</sup> Because *Streptococcus pneumoniae* serotypes are diverse and vary in frequency, monitoring of invasive disease serotypes remains important for immunization programs.

PCV7 was licensed in Canada in June 2001 and is recommended for all children under the age of 2 years and for children 2 to 4 years at high risk for disease.<sup>7</sup> Alberta began universal use of the vaccine in infants born after July 2002, followed by British Columbia from July 2003. Both provinces recommended vaccination at 2, 4 and 6 months; neither provided catch-up vaccination to older, healthy infants. The remaining provinces started universal infant programs in 2005. The 23-valent polysaccharide vaccine (PPS) is recommended for all high-risk children age 5 and older, and can be used from age 2 to reinforce and expand protection provided by PCV7.<sup>1,8</sup>

Before 1990 in Canada, almost all pneumococcal isolates were susceptible to penicillin. Since then, an increasing proportion of pneumococcal isolates has reduced susceptibility to penicillin and other antibiotics.<sup>9</sup>

We conducted active surveillance for invasive pneumococcal disease from 1998-2003 to assess the serotype and antibiotic resistance patterns in Canadian children. We previously reported data from 1991-1998.<sup>10</sup> This report provides more recent data on serotyped cases in children. We determined the degree of matching between PCV7, PPS and disease serotypes

TABLE I

Pneumococcal Infections by IMPACT Hospital, January 1998 – December 2003

IMPACT Centre	1998	1999	2000	2001	2002	2003	Total (%) N=1821	Mean, 95% CI
St. John's	2	8	5	3	9	8	35 (1.9)	6, 2.8-8.9
Halifax	14	15	12	11	14	10	76 (4.1)	13, 10.6-14.7
Quebec City	16	8	21	24	18	16	103 (5.5)	17, 11.4-22.9
Montreal A*	38	37	40	31	30	21	197 (10.6)	33, 25.5-40.2
Montreal B*	62	60	36	30	40	37	265 (14.2)	44, 30-58.3
Ottawa	25	30	35	31	27	35	183 (9.8)	31, 26.2-34.8
Toronto	36	37	34	54	36	38	235 (13.0)	39, 31.4-47
Winnipeg	10	12	30	23	22	28	125 (6.7)	21, 12.2-29.5
Saskatoon†	—	16	15	20	18	16	85 (4.6)	17, 14.5-19.5
Edmonton‡	21	24	28	25	31	35	164 (8.8)	27, 22-32.7
Calgary‡	14	19	21	39	29	17	139 (7.4)	23, 13.5-32.9
Vancouver§	44	47	38	33	57	42	261 (14.0)	44, 34.9-52
TOTAL	282 (15.1)	313 (16.8)	315 (16.9)	324 (17.3)	331 (17.7)	303 (16.2)	1868 (100)	303.5 293.2-329.5

\* Montreal A and B represent two different children's hospitals in Montreal.

† Surveillance started in Saskatoon in 1999.

‡ Pneumococcal conjugate vaccine was provided from 2 months of age to children born after July 1, 2002, § or July 1, 2003.

TABLE II

Pneumococcal Serotypes (Percent) Matching PCV7 and PPS23 by Age, 1998-2003

	1998	1999	2000	2001	2002	2003	Total	P-value
Serotypes matching 7-valent pneumococcal conjugate vaccine*	229 (81.2)	254 (81.2)	256 (81.3)	258 (79.6)	253 (76.4)	222 (73.3)	1472 (78.8)	0.005
in 0-5 month olds	10 (58.8)	23 (79.3)	23 (69.7)	21 (80.8)	17 (68.0)	14 (58.3)	108 (70.1)	0.537
in 6-23 month olds*	121 (87.7)	153 (89.0)	147 (88.0)	127 (83.0)	135 (80.4)	107 (75.4)	790 (84.0)	0.002
healthy*	105 (90.5)	129 (92.1)	110 (89.4)	99 (84.6)	107 (82.3)	79 (77.5)	629 (86.4)	0.002
in 2-5 year olds	80 (88.9)	61 (72.6)	65 (81.3)	82 (80.4)	75 (79.0)	81 (77.9)	444 (80.0)	0.269
in 6-9 year olds	14 (60.9)	12 (66.7)	14 (60.9)	21 (75.0)	19 (70.4)	12 (60.0)	92 (66.2)	0.716
in 10-16 year olds	4 (29.0)	5 (50.0)	7 (58.3)	7 (46.7)	7 (43.8)	8 (61.5)	38 (47.5)	0.231
Serotypes matching 23-valent pneumococcal polysaccharide vaccine	115 (90.6)	96 (85.7)	104 (90.4)	136 (93.8)	118 (85.5)	124 (90.5)	693 (89.5)	0.958
in 2-5 year olds	84 (93.3)	69 (82.1)	73 (91.3)	96 (94.1)	80 (84.2)	97 (93.3)	499 (89.9)	0.725
in 6-9 year olds	20 (86.4)	18 (100)	22 (95.5)	27 (96.4)	24 (88.9)	17 (84.2)	128 (92.1)	0.470
in 10-16 year olds	11 (78.6)	9 (90.0)	9 (75.0)	13 (86.7)	14 (87.5)	10 (76.9)	66 (82.5)	0.945

\* significant trend ( $p \leq 0.05$ )

and penicillin-resistant isolates, prior to the widespread implementation of universal infant immunization programs.

## METHODS

Active surveillance was conducted by the 12 centres of the Canadian Paediatric Society's Immunization Monitoring Program, Active (IMPACT). These centres are located across Canada, admit over 75,000 children annually and account for nearly 90% of the nation's tertiary care pediatric beds. The centres serve a population base of about 20% of Canada's children.<sup>11</sup> Surveillance has been continuous at 10 centres since 1991 and at 12 centres since 1999. All centres used the same case-finding strategies, case definition and report form. Information on the case report form included the patient's age, sex, pneumococcal immunization history and prior health – including any pre-existing medical conditions, which encompassed those known to be risk factors for pneumococcal infection – the extent of the current

pneumococcal infection, the sources of positive cultures and the outcome.

Inclusion in the surveillance required isolation of *S. pneumoniae* from a normally sterile site (e.g., blood, CSF, pleural fluid). Cases were not captured if a stored isolate was unavailable or non-viable. Both inpatients and outpatients were included. Centres forwarded isolates (1 per case) to the National Centre for Streptococcus (NCS) in Edmonton, Alberta, where they were serotyped by Quellung reaction using pneumococcal type specific antisera (Statens Seruminstitut, Copenhagen).<sup>12</sup> All isolates were assayed at the NCS for non-susceptibility to penicillin and cefotaxime or ceftriaxone according to NCCLS guidelines.<sup>13</sup> Intermediate-level penicillin resistance was defined as an MIC (minimum inhibitory concentration) 0.1-1.0 µg/mL and high-level resistance at an MIC  $\geq 2.0$  µg/mL. Resistance to cefotaxime/ceftriaxone was defined as an MIC  $\geq 2.0$  µg/mL.

The proportions of isolate serotypes that matched PCV7 and PPS were analyzed for

trends over the six-year period overall, by age, gender, pre-existing medical conditions, season and IMPACT centre. Differences in PCV7 matching were examined for centres with a universal immunization program (BC, Alberta). Rates of penicillin non-susceptibility and cefotaxime/ceftriaxone resistance were examined for trends over the six-year period overall and by age, health status and universal immunization programs and the average rates were compared to the previously published IMPACT report.<sup>14</sup> SAS version 8.02 (SAS Institute, Cary, NC) was used for all analyses. Categorical variables were tested with chi-square and Fisher exact tests, and temporal trends were tested with Mantel-Haenszel chi-square.

## RESULTS

During the six years of surveillance, 1,868 eligible cases were reported. Of these, 154 (8.2%) cases occurred in 0-5 month olds,

TABLE III

Cases (Percent) with Specific PCV7 Serotypes and Related Serotypes, 1998-2003

Serotype	1998	1999	2000	2001	2002	2003	Total	P-value
14	77 (27.3)	87 (27.8)	92 (29.2)	89 (27.5)	76 (23.0)	70 (23.1)	491 (26.3)	0.071
6B	45 (16.0)	54 (17.3)	43 (13.7)	54 (16.7)	55 (16.6)	39 (12.9)	290 (15.5)	0.423
19F	36 (12.8)	32 (10.2)	42 (13.3)	39 (12.0)	37 (11.2)	41 (13.5)	227 (12.2)	0.726
18C	28 (9.9)	26 (8.3)	28 (8.9)	29 (9.0)	31 (9.4)	29 (9.6)	171 (9.2)	0.893
9V	6 (2.1)	18 (5.8)	17 (5.4)	17 (5.3)	20 (6.0)	14 (4.6)	92 (4.9)	0.230
4	12 (4.3)	10 (3.2)	13 (4.1)	20 (6.2)	16 (4.8)	14 (4.6)	85 (4.6)	0.366
23F*	25 (8.9)	27 (8.6)	21 (6.7)	10 (3.1)	18 (5.4)	15 (5.0)	116 (6.2)	0.005
6A†	12 (4.3)	15 (4.8)	12 (3.8)	11 (3.4)	14 (4.2)	21 (6.9)	85 (4.6)	0.270
19A†	8 (2.8)	6 (1.9)	7 (2.2)	7 (2.2)	5 (1.5)	11 (3.6)	44 (2.4)	0.715

\* significant trend ( $p \leq 0.05$ )

† PCV7 related serotypes

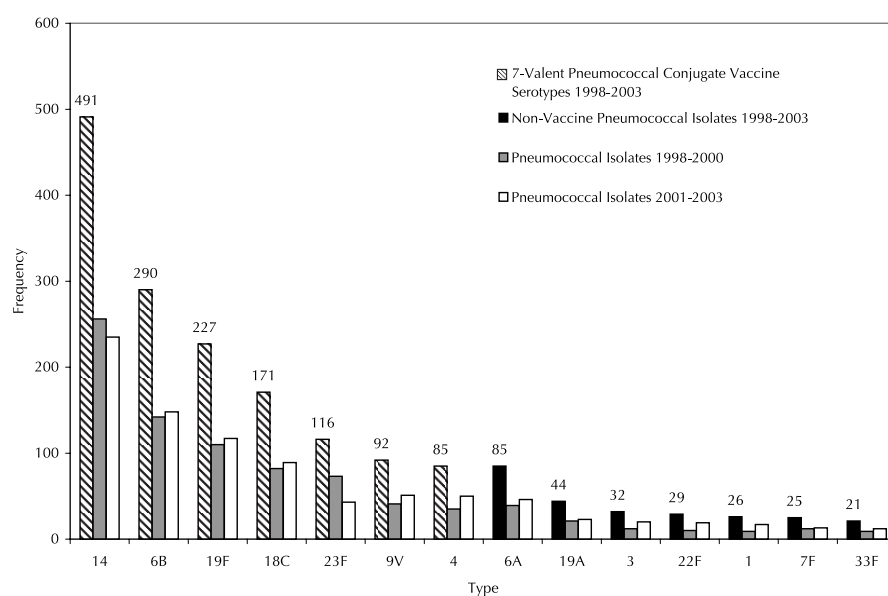


Figure 1. Serotype distribution of IMPACT pneumococcal isolates

940 (50.3%) in 6-23 month olds, 555 (29.7%) in 2-5 year olds, 139 (7.4%) in 6-9 years olds and 80 (4.3%) in 10-16 year olds. Before developing pneumococcal infection, 69% of children were considered healthy, while 31% had at least one underlying medical condition. A total of 52 (2.8%) cases were immunized; 40 had a risk factor for infection. Overall, 1,281 (68.6%) cases were admitted to hospital. The most common manifestations of pneumococcal infection were bacteremia (35.4%), pneumonia (25.8%), meningitis (15.1%), otitis media (14.8%) and seizures (9.9%). Fifty-three (2.8%) cases resulted in death. Case fatality rates were 5.2% in 0-5 month olds, 2.5% in 6-23 month olds, 1.6% in 2-5 year olds, 2.9% in 6-9 year olds and 10% in 10-16 year olds. Those most likely to die were children under 2 years of age, who accounted for 60% (32 of 53) of the fatalities. However, 15% of deaths occurred in children after age 9, although this age group accounted for only 4.3% of cases. Most deaths in this age

group (6 of 8) occurred in children with pre-existing medical conditions.

No significant differences appeared in case prevalence across Canada from year to year (Table I), including the years 2001 to 2003 after PCV7 was licensed and gradually introduced across Canada. Distribution of cases overall and by centre is shown in Table I. Additionally, no significant differences were found in the distribution of cases across Canada by age group from year to year, including 2001-2003 (data not shown). Seasonal variation occurred in the number of cases with a significant difference between cases in summer and winter (16.2% during July through September vs. 31.7% during October through December).

Isolates were from blood (1,547; 82.8%), CSF (55; 3.0%), pleural fluid (27; 1.5%), joint fluid (16; 0.9%), deep abscess (7; 0.5%), peritoneal fluid (2; 0.1%), or other sterile sites (11; 0.6%). Serotype data were available for all isolates. Isolates represented a total of 42 serotypes or

serogroups, for which the partial frequency distribution is presented in Figure 1. Only two isolates were non-typable. Serotype distribution did not differ significantly by gender or season. PCV7 matched 78.8% of isolates, including 70.1% in 0-5 month olds, 84.0% in 6-23 month olds, 80.0% in 2-5 year olds, 66.2% in 6-9 year olds and 48.0% in children 10 years or older. The match rate was almost equal for males and females (79.5% vs. 78.0%). When we examined the match rate by age group and health status, we found a significant difference only among 6-23 month olds where the match rate was significantly better in cases without a pre-existing medical condition (86.4%) than in those with a pre-existing condition (75.9%). The majority of bacteremia cases (82.8%), pneumonia (72.8%) and meningitis cases (77.0%) matched PCV7. A total of 36 (68.0%) deaths were caused by a serotype found in PCV7 and 19 of these deaths occurred in children 6-23 months old, 7 of whom had a pre-existing medical condition.

The proportion of isolates matched by PCV7 each year significantly decreased over the surveillance period, 81.3% in 2000 to 73.3% in 2003 (Table II). Across Canada in 6-23 month olds, the same trend was shown, even when adjusted for health status (Table II). While some decreases were evident in other age groups, no significant trend was found. We found no significant trend in the yearly proportion of isolates matching PCV7 at any of the centres (data not shown); including those with recently implemented universal vaccine programs (BC, AB). When we looked at each serotype in PCV7 individually to determine if a change in one serotype was driving the decrease in matching (Table III), we found a significant trend in 23F, which went from 25 (9.0%) isolates in 1998 to 15 (5.0%) in 2003.

Other serotypes in PCV7 (14, 6B, 19F, 18C, 9V and 4), including cross-reacting types (6A and 19A) were not significantly different in frequency over the 6 years.

Considering PCV7-related serotypes (6A and 19A), the overall match increased to 85.7% and was 91.0% among 6-23 month olds. PPS matched 89.5% of serotypes from children 2 years or older (Table II). The match did not change significantly over the 6-year period in any age group for either vaccine (Table II). Finally, we examined the most common non-vaccine serotypes (6A, 19A, 3, 22F, 7F, 1 and 33F) over the time period and found no significant differences over the 6 years (Figure 1).

Penicillin non-susceptibility was detected in 303 (16.2%) isolates, with 185 (10.0%) having intermediate and 118 (6.3%) high resistance. Children with an underlying medical condition were significantly more likely to be infected with penicillin non-susceptible isolates (19.3% vs. 14.8% in healthy children). Overall, the yearly range was 36 (12.8%) to 64 (19.3%) isolates, and no significant trend was found, even when adjusted for underlying health status. Additionally, no significant differences by age alone or age adjusted for health status were found (data not shown). Cefotaxime/ceftriaxone resistance was detected in 92 (4.9%) isolates from across Canada and limited to penicillin non-susceptible isolates. No significant differences were found by health status (5.5% vs. 4.6% in healthy children). Serotypes found in PCV7 accounted for 89.4% of penicillin-resistant isolates (99.7% including cross-reacting types 6A and 19A), and 95.0% of cefotaxime/ceftriaxone resistant isolates (100% including cross-reacting types 6A and 19A). Serotypes in PPS matched 92.9% of penicillin-resistant isolates and 96.2% of cefotaxime/ceftriaxone resistant isolates from children 2 years or older.

## DISCUSSION

Our case series data illustrate the burden of invasive pneumococcal disease in Canadian children prior to universal infant pneumococcal immunization programs. While we expect to see a rapid and substantial reduction in disease as a result of these new programs,<sup>15-17</sup> the effect may not be as extensive as predicted.

## Appendix

### Investigators and centres participating in this IMPACT project included:

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Over the last 6 years, a shift occurred in the serotypes of isolates from the 6-23 month age group, with fewer matching PCV7. This shift appears to be a spontaneous decrease in one serotype (23F) and not associated with vaccine use, as it predates the implementation of universal immunization programs, did not occur in any other vaccine serotypes and was not driven by infections in children with pre-existing medical conditions. The shift demonstrates the inherent instability of pneumococcal serotypes,<sup>2,6,18-21</sup> suggests the direct cost-effectiveness of the new vaccine programs may not be as high as predicted,<sup>22-25</sup> and indicates that vaccine failures are inevitable – cases will occur in spite of immunization. The rate of penicillin non-susceptible isolates almost tripled since our previous report of 6.8% from 1991-1998<sup>10</sup> to our current reported rate of 16.4%. The high proportion of matching between penicillin and cefotaxime/ceftriaxone resistant isolates and PCV7 and PPS indicates that immunization could provide an effective solution to the increase in resistant disease, a result that has been evident in recent US (United States) reports.<sup>15,16,26,27</sup>

The centres involved in the surveillance have undefined referral populations precluding accurate calculation of disease incidence rates. Our surveillance is conducted in major tertiary care hospitals and may over-represent children with pre-existing conditions. Although outpatient and inpatient cases were included to provide a more representative hospital sample, they may not fully reflect the community experience. The number of cases at each centre was small, thus making any centre-specific conclusions difficult. Secular trends may exist in our data; however we did not discover changes in referral patterns or pneumococcal diagnosis over the surveillance period.

Continued monitoring of invasive pneumococcal serotype patterns and antibiotic resistance as well as centralized isolate testing to detect vaccine failures will be necessary to determine the effects of universal PCV7 immunization programs. Shifts to non-vaccine-related strains and an increase in resistance in non-vaccine serotypes have been shown in the US<sup>28,29</sup> and may occur in Canada. Finally, the high case fatality rates in children over the age of 5 years indicate a need for renewed emphasis on immunization with PPS for older children with chronic conditions, who need individual attention from vaccine providers.

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## RÉSUMÉ

**Contexte :** Nous avons effectué une surveillance active des maladies invasives à pneumocoques pour analyser les sérotypes et les structures d'antibiorésistance au Canada avant l'instauration des programmes de vaccination universelle des nourrissons dans la plupart des provinces.

**Méthode :** Une surveillance active a été effectuée par les 12 centres IMPACT (Programme canadien de surveillance active des effets secondaires associés aux vaccins) de la Société canadienne de pédiatrie. Notre article porte sur des enfants de 16 ans et moins atteints de la souche *S. pneumoniae* isolée sur un site normalement stérile entre 1998 et 2003.

**Résultats :** Durant les six années de surveillance, 1 868 cas admissibles ont été signalés. Les sérotypes du vaccin antipneumococcique conjugué heptavalent (VCP7) correspondaient à 79 % des isolats, dont 84 % chez les nourrissons de 6 à 23 mois et 80 % chez les enfants de 2 à 5 ans. La proportion d'isolats correspondant au VCP7 a sensiblement diminué au cours de la période de surveillance, passant de 81 % en 1998 à 73 % en 2003 ( $p=0,005$ ). Les sérotypes du vaccin polysaccharidique 23-valent correspondaient à 90 % des isolats des enfants de 2 ans et plus. Le taux d'absence de sensibilité à la pénicilline (16 % des isolats) est resté stable. Le taux de résistance au céfotaxime/à la ceftriaxone (5 %) n'a été observé que dans les isolats résistants à la pénicilline. Les sérotypes contenus dans le VCP7 comptaient pour 89 % des isolats résistants à la pénicilline (100 % incluant les types récurrents 6A et 19A).

**Conclusion :** Les sérotypes du VCP7 ne couvraient que les trois quarts des isolats chez les jeunes enfants au début des programmes d'immunisation; certains échecs de la vaccination étaient donc inévitables. Les enfants de 5 ans et plus dont l'état de santé les prédisposait aux infections ont besoin de la protection accrue du vaccin 23-valent, et les vaccinateurs doivent s'assurer que ce vaccin leur a été administré. Le taux de résistance à la pénicilline est resté stable au cours des six dernières années. La majorité des isolats non réceptifs à la pénicilline se trouvent dans le VCP7.