Epidemiology of Invasive Pneumococcal Disease in BC during the Introduction of Conjugated Pneumococcal Vaccine

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ABSTRACT

Objectives: Antimicrobial resistance in *Streptococcus pneumoniae* has increased in recent decades. We linked two surveillance programs to evaluate trends in incidence, serotype distribution, and antimicrobial resistance in invasive pneumococcal disease (IPD) since the heptavalent pneumococcal conjugate vaccine (PCV7) was introduced in BC in 2003.

Methods: IPD case reports for BC from 2002-2005 from the BC Centre for Disease Control were linked to serotype and antimicrobial susceptibility results from the National Centre for Streptococcus (NCS).

Results: There was a significant decrease in IPD incidence in children <5 from 54/100,000 in 2002 to 16/100,000 population in 2005 (70% decrease, p<0.001). The most dramatic decline was in children aged 1 year, where the rate fell from 135/100,000 to 15/100,000 (89% decrease, p for trend <0.001). Overall, 728/1288 (56.5%) reported cases of IPD were referred to NCS. For all matched cases, the proportion of isolates of PCV7 preventable serotypes decreased from 68.9% to 43.8% (p for trend <0.001) between 2002 and 2005. In children <2 years, this proportion decreased from 83.0% (39/47 cases) to 16.7% (1/6 cases) (p=0.006). The prevalence of non-susceptible isolates was highest for trimethoprim-sulfamethoxazole (15.3%, 111/725 tested), penicillin (9.1%, 66/728), and erythromycin (9.1%, 66/727). 10.3% (75/728) were non-susceptible to ≥2 classes of antimicrobials. Children <15 years of age had the highest proportion of non-susceptible isolates.

Discussion: The incidence of IPD in children has decreased significantly since the introduction of PCV7. Comprehensive serotype and antimicrobial susceptibility can aid in evaluating the impact of immunization programs.

Key words: Pneumococcal infections; antimicrobial drug resistance; pneumococcal vaccines; Canada

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

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The rates of antimicrobial resistance to most infectious diseases are rising.[1] Alarming increases in drug and multidrug resistance have been observed in community-acquired pathogens.[2,3] In Canada, the annual economic burden of resistance is estimated at $200 million.[4]

Antimicrobial resistance in *Streptococcus pneumoniae*, the leading bacterial cause of community-acquired pneumonia, meningitis and otitis media, is highly variable geographically. In North America, surveillance programs of clinical isolates have shown increasing resistance since the 1980s, with the proportion of penicillin-resistant isolates at 15% in Canada in 2002,[5] and 25% in the US.[6] With the high incidence, morbidity and mortality of invasive pneumococcal disease (IPD), increasing rates of antimicrobial resistance are of particular concern for public health.

The 7-valent pneumococcal conjugate vaccine (PCV7) covers 80% of serotypes causing invasive disease in children under 5 years.[7] It was licensed for use in Canada in 2001 and a universal infant program was initiated in BC in 2003. Thus far, national surveillance on antimicrobial resistance has only included a limited number of isolates from western Canada.[5,8,9] In this study, we linked reported cases with serotype and antimicrobial susceptibility results over 2002-2005 to obtain a more complete picture of the epidemiology of IPD in BC.

METHODS

Case reports

IPD, defined as the isolation of *S. pneumoniae* from a sterile site – usually in the form of blood or cerebrospinal fluid – is a reportable disease. The procedure in BC is for laboratory-confirmed cases to be reported to the local Medical Health Officer and recorded in the Integrated Public Health Information System (iPHIS), and for isolates to be referred to laboratory at the BC Centre for Disease Control (BCCDC). We extracted case reports for invasive disease (pneumococcal meningitis and other invasive pneumococcal disease) for 2002-2005. These years were selected based on a consistent case definition and pattern of referral to the National Centre for Streptococcus (NCS).

Preliminary reports on incidence in BC are reported elsewhere.[10] The database steward and research board at BCCDC approved this research.

Serotyping and susceptibility testing

Invasive isolates are routinely referred by BCCDC to the NCS for serotyping and antimicrobial susceptibility. Serotyping is based on the quellung reaction using commercial antisera obtained from the Statens Seruminstitut, Copenhagen, Denmark. We considered isolates to be PCV7 type (serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F) or not ("non-PCV7"), as well as 23-valent polysaccharide vaccine (PPV23) type or not. Minimum inhibitory concentrations (MICs) for 9 antimicrobials (penicillin, cefotaxime, chloramphenicol, erythromycin, levofloxacin, ofloxacin, clindamycin, trimethoprim-sulfamethoxazole and vancomycin) were determined by broth microdilution, and interpreted according to standard guidelines.[11] 'Non-susceptible' includes isolates with either intermediate or high resistance; 'multidrug resistance' is defined as non-susceptible to ≥2 antimicrobial classes.

Linkage

For linkage purposes, we reviewed demographics to ensure a unique record per person in each database. Case year was defined according to the date of specimen collection. In 5% of cases where this was missing, the year was imputed based on case report date. Records were linked by last name and date of birth, and anonymized for analysis.

Analysis

Annual cumulative incidence rates of IPD, reported as the number of cases per 100,000 population, were calculated using the P.E.O.P.L.E. 30 Population Estimates and Projections[12] using all iPHIS case reports (n=1288). The linked study sample consisted of matched records (n=728). Differences between matched and unmatched records were compared using chi-square tests or Fisher's exact tests in SAS (version 9.1; SAS Institute). Chi-square tests for trends in the proportion of PVC7 serotypes and of non-susceptible isolates were conducted in Epi-Info (version 6.03; US CDC) with 2-sided p-value <0.05 considered significant.

TABLE I

Rate of Reported Cases of Invasive Pneumococcal Disease (per 100,000 population) in BC, 2002-2005

Age (years)	2002	2003	2004	2005
		(Cases per 100,000 population)		
<1*	50.6	57.3	15.1	20.1
1*	134.7	105.5	66.5	14.9
2*	40.4	31.6	17.4	12.2
3	27.9	23.6	29.0	27.1
4*	22.7	16.2	11.7	7.2
All ages	8.3	7.7	7.5	7.7

* Chi-square test for trend significant at p<0.05

TABLE II

Distribution of IPD Cases According to Age, Sex, and Year for Matched* and Unmatched† iPHIS Records in BC, 2002-2005

	Matched Records		Unmatched Records	
	n	%	n	%
Total cases	**728**	**100**	**560**	**100**
Age‡				
<15	239	33	119	21
15-64	319	44	234	42
>64	170	23	207	37
Female	333	46	260	46
Year of Case				
2002	181	25	159	28
2003	191	26	124	22
2004	179	25	138	25
2005	177	24	139	25

* isolates which have records of matching last name and date of birth in the Integrated Public Health Information System (iPHIS) at BCCDC and at the National Centre for Streptococcus (NCS).
† isolates which have records in iPHIS, but not in NCS.
‡ significantly different (p<0.05) distribution for matched versus unmatched records.

RESULTS

Prior to the 2003 commencement of the universal infant program, the overall rate of IPD in BC was 8.3 cases per 100,000 population, and highest in 1 year olds. Between 2002 and 2005, there was a significant decrease in the incidence in children ≤5 from 54.4 to 16.2/100,000 (p<0.001). Table I shows the rate of reported cases of IPD in BC overall, and by year of age within the <5 age group.

Overall population rates of reported IPD have been relatively stable (7.5-8.3/100,000). The rate of IPD was high in the ≥65 age group, ranging from 15.8/100,000 in 2002 to 19.6/100,000 in 2005 (trend not statistically significant).

In the linkage, 728 (56.5%) IPD iPHIS reports had matching NCS records. Table II shows the distribution of matched and unmatched records according to demographics. Referred isolates tended to be from younger individuals compared to non-referred isolates.

In addition, 200 isolates tested at NCS did not have corresponding iPHIS case reports. A greater proportion of the referred isolates were from younger individuals. These were less likely to be PCV7 serotypes, but did not differ in terms of year of the case, or susceptibility (data not shown).

Serotype trends

Serotype results were available for 98.2% (715/728) of matched isolates. 13 isolates were "non-typable" (i.e., no capsule could be demonstrated) and were excluded. Overall, 56.6% (405/715) were of PCV7 serotypes. Isolates from children <5 years (n=194) were 25 different serotypes, of which 76.8% (n=149) were PCV7 types. Isolates from ≥5 years population (n=521) had more variability in serotype (45 types), with 49.1% (n=256) of PCV7 types and 86.0% (n=448) of PPV23 types. In children <2 years, the population eligible for universal PCV7 immunization, the proportion of cases with PCV7 serotypes decreased significantly over 2002-2005 from 83.0% (39/47 cases) to 16.7% (1/6 cases) (p for trend=0.006) (Figure 1). Similar results were observed in the overall population

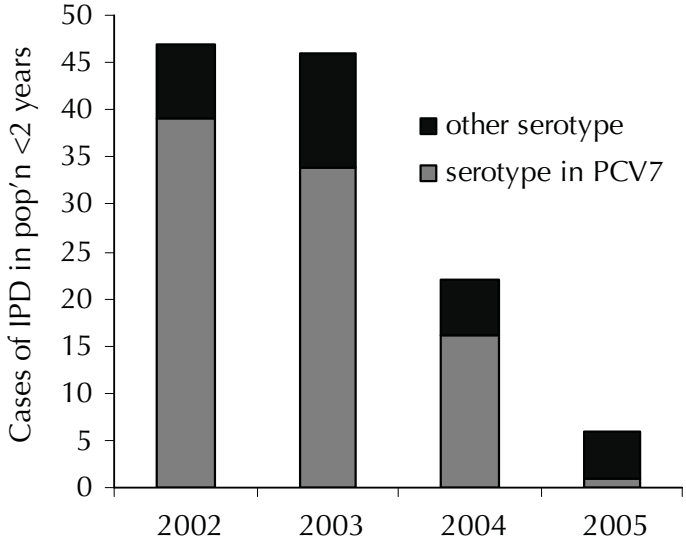

Figure 1. Reported cases of invasive pneumococcal disease in the population <2 years in BC over 2002-2005, by serotype status

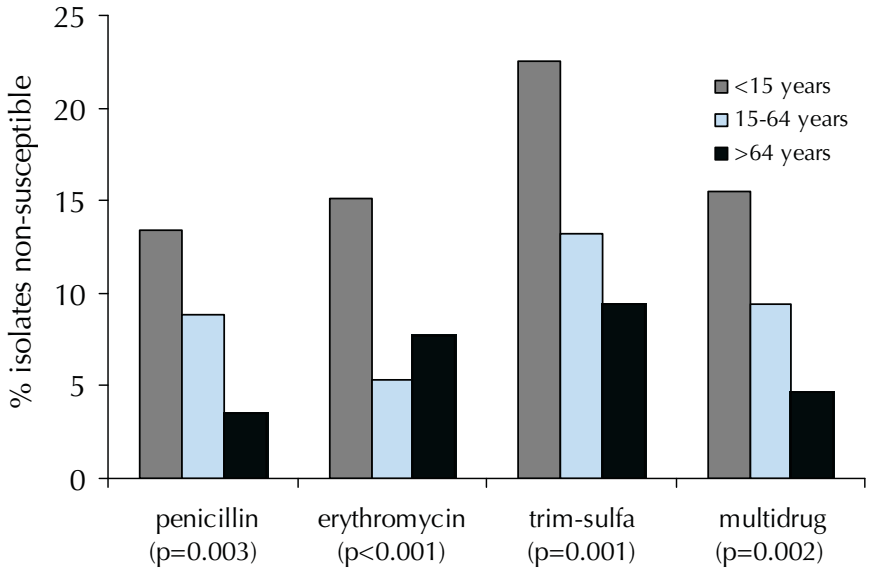

Figure 2. Proportion of invasive pneumococcal isolates (n=564) non-susceptible to penicillin, erythromycin, trimethoprim-sulfamethoxazole and multiple drug classes by age group in BC, 2002-2005
p for trend in brackets

(from 68.9% to 43.8%, p for trend <0.001). There were no significant changes in the proportion of PPV23 serotypes.

Antimicrobial resistance trends

Overall, 22.8% (166/728) of matched isolates were non-susceptible to at least one antimicrobial. The prevalence of non-susceptible isolates was highest for trimethoprim-sulfamethoxazole (15.3%, 111/728), penicillin (9.1%, 66/728), and erythromycin (9.1%, 66/727). Non-susceptibility to other antimicrobials was low: clindamycin (4.3%, 31/727), chloramphenicol (1.0%, 7/720), cefotaxime (0.3%, 2/725), and no isolates were non-susceptible to vancomycin. For fluoroquinolones, 7.6% (9/118 isolates tested) were non-susceptible to ofloxacin and 0.6% (4/55) to levofloxacin.

A total of 75 (10.5%) of isolates were found to be multidrug resistant. Of these, 63 (85.6%) were non-susceptible to trimethoprim-sulfamethoxazole, 59 (78.7%) to penicillin, and 37 (49.3%) to erythromycin.

Figure 2 illustrates susceptibility patterns by age, and Figure 3 by year. Isolates from those under 15 years had the highest proportion of non-susceptibility. There were no significant trends by year over 2002-2005.

Non-susceptibility was more frequent in vaccine serotypes. Of the penicillin non-susceptible isolates, 69.2% (45/65) were PCV7-type, compared to only 55.4% (360/650) (p=0.032) of penicillin-susceptible isolates. Penicillin non-susceptibility was also observed for non-PCV7 serotypes 19A (20.0% of non-susceptible isolates), 35B, 6A, 15A and 1 (total of 30.8% of non-susceptible isolates). Similarly for erythromycin, 69.7% of the non-susceptible isolates (46/66) were PCV7-type, compared to only 55.4% (359/648) of susceptible isolates (p=0.025).

DISCUSSION

This study shows a decrease in the incidence of reported cases of IPD in younger age groups following the introduction of the PCV7 vaccine in 2003. Furthermore, it demonstrates a significant decline in the proportion of PCV7 serotype isolates in children under 2 years, and in the overall population. Children under 15 years had the highest rates of non-susceptibility to penicillin, erythromycin, trimethoprim-sulfamethoxazole and to multiple antimicrobials.

The most dramatic reductions in incidence occurred in those <2 years of age. A similar observation was made after the introduction of PCV7 in the US in 2000. Results from the Active Bacterial Core Surveillance program for 13,568 cases of IPD found the largest impact in children aged 1, where IPD rates fell by 69% from 168.1/100,000 in 1998/1999 to 52.3/100,000 in 2001.[13] Significant declines in incidence were also reported for adult and elderly age groups. Subsequent studies in the US indicate that these trends have continued through 2004.[14,15] However, we observed increasing (though not statistically significant) incidence in the ≥65 age group. There are several possible reasons we did not see a similar decline. First, the US program was introduced earlier with more opportunity for catch-up, and thus a greater chance to demonstrate herd immunity. Alternatively, there may

be different levels of use of the PCV7 or PPV23 between BC and the US (unpublished data, BCCDC),[16-18] better health status in seniors or differing surveillance techniques. Any of these reasons could limit the ability to detect an early decline in IPD in the elderly in Canada.

This is the first population-based study on antimicrobial resistance for BC. We found no annual trends in antimicrobial resistance over 2002-2005, which differs from reports of increasing rates in preceding years in Canada[5,19] and the US.[6] National estimates from the Canadian Bacterial Surveillance Network (CBSN), based on voluntarily reported isolates, show an upward trend in erythromycin resistance, from 2% in 1993 to 19% in 2005.[20] While results for BC specifically are based on fewer isolates, the general trend is similar.[21] Our results may differ from CBSN or the US as the current study covered only four years (a period defined by consistent reporting and referral), or because vaccine uptake may be slower in BC. Also, isolates' origins differ in that CBSN includes non-invasive isolates (>50% of isolates in 2002). This may be significant as serotype and susceptibility patterns differ between invasive and non-invasive disease.[22]

Our results show that the PCV7 serotypes are more likely to be non-susceptible than non-vaccine serotypes. This indicates potential for the vaccine to reduce the burden of resistant disease, especially in children, where the proportion of non-susceptible disease is higher. Such a phenomenon was reported in the US[15] where, between 1999 and 2004, the rates of penicillin non-susceptible isolates fell by 81% in children <2, and by 49% in adults >65 years. While these data cover only 2 years since the vaccine was introduced in BC, we saw no continued increase in the proportion of non-susceptible isolates. This shift may mark the beginning of the impact of the vaccine in Canada; future years may bring significant declines in resistant disease, in keeping with trends in the US.

Surveillance results are key to creating and evaluating evidence-based public health policies, but must be interpreted with care. The generalizability of these findings depends on degree of coverage of the two surveillance programs. We expected that reporting rates for IPD were high; however, this linkage revealed that 200 isolates from BC tested at NCS were not reported to iPHIS, suggesting that some hospitals may refer isolates directly to NCS, bypassing BCCDC. Since susceptibility patterns did not differ between NCS isolates with or without iPHIS reports, our results should be representative in this regard. Additionally, only 56% of iPHIS reports had isolates referred from BCCDC to NCS, and these tended to be from younger individuals. A possible explanation is that those non-referred iPHIS reports were not accompanied by an isolate submission (to either BCCDC or NCS). With improved commitment to reporting and referral, estimates from surveillance programs would be increasingly accurate.

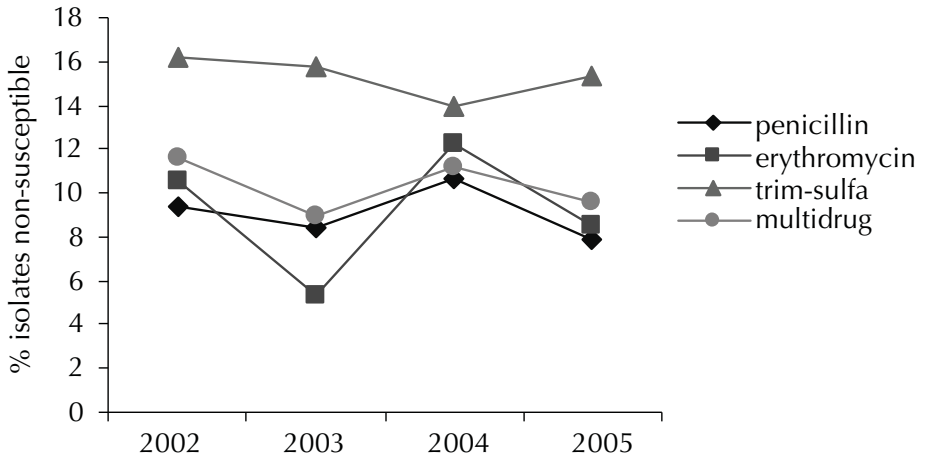

Figure 3. Proportion of invasive pneumococcal isolates with reduced susceptibility to penicillin, erythromycin, trimethoprim-sulfamethoxazole and multiple drug classes over 2002-2005

Certain questions could not be addressed due to data limitations. iPHIS records cover all reported cases, but do not contain the clinical diagnosis (i.e., pneumonia, bacteremia) or the infection origin (hospital or community-acquired). Finally, while the antimicrobial resistance surveillance is important for public health protection, the clinical significance of in vitro resistance is not yet clear,[23-26] although as the proportion of isolates with higher MICs rises, there is likely to be greater clinical impact.

In summary, this linkage of surveillance systems provides detailed information on the epidemiology of IPD in BC. Since the introduction of PCV7, there has been a dramatic reduction in the incidence in children under 5 years and significant shifts in the distribution of serotypes away from PCV7 types, especially in children under 2 years. The proportion of isolates non-susceptible to penicillin, erythromycin, trimethoprim-sulfamethoxazole, and to multiple antimicrobials has not increased over 2002-2005, but the highest rates were found in children <15 years. With the new conjugate vaccine, and programs aimed to reduce antimicrobial usage in the community, continued surveillance is necessary to monitor the impact of initiatives on rates of resistant disease. Testing all invasive isolates for serotype and antimicrobial susceptibility would provide a more complete evidence base for public health decision-making.

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RÉSUMÉ

Objectifs : Depuis quelques décennies, la résistance aux antimicrobiens contre *Streptococcus pneumoniae* est en hausse. Nous avons relié deux programmes de surveillance afin d'évaluer les tendances relatives à l'incidence, à la distribution des sérotypes et à la résistance aux antimicrobiens pour les maladies invasives à pneumocoques (MIP) depuis l'introduction du vaccin antipneumococcique conjugué heptavalent (VCP7) en Colombie-Britannique en 2003.

Méthode : Les cas de MIP déclarés en Colombie-Britannique de 2002 à 2005, obtenus du BC Centre for Disease Control, ont été liés aux résultats par sérotype et par sensibilité aux antimicrobiens du Centre national pour le streptocoque (CNS).

Résultats : Nous avons observé une diminution significative de l'incidence des MIP chez les enfants de moins de 5 ans, qui est passée de 54 p. 100 000 en 2002 à 16 p. 100 000 en 2005 (soit une baisse de 70 %, p<0,001). La chute la plus spectaculaire a été observée chez les enfants d'1 an, chez qui les taux sont passés de 135 p. 100 000 à 15 p. 100 000 (soit une baisse de 89 %, p<0,001). Globalement, 728 des 1 288 cas déclarés de MIP (56,5 %) ont été dirigés vers le CNS. Pour tous les cas assortis, la proportion des isolats de sérotypes évitables par le VCP7 a diminué, passant de 68,9 % à 43,8 % (p<0,001) entre 2002 et 2005. Chez les enfants de moins de 2 ans, cette proportion est passée de 83 % (39 cas sur 47) à 16,7 % (1 cas sur 6) (p=0,006). La prévalence des isolats résistants était la plus élevée pour le triméthoprime-sulfaméthoxazole (15,3 %, 111/725), la pénicilline (9,1 %, 66/728) et l'érythromycine (9,1 %, 66/727). Une proportion de 10,3 % (75/728) des isolats étaient résistants à 2 classes ou plus d'antimicrobiens. Les enfants de moins de 15 ans avaient la proportion la plus élevée d'isolats résistants.

Discussion : L'incidence des MIP chez les enfants a diminué de façon significative depuis l'introduction du VCP7. L'inclusion de tous les sérotypes et la sensibilité aux antimicrobiens sont deux éléments qui peuvent faciliter l'évaluation des impacts des programmes d'immunisation.

Mots clés : infections à pneumocoques; résistance aux antimicrobiens; vaccins antipneumococciques; Canada