The Epidemiology of Invasive Pneumococcal Disease in British Columbia Following Implementation of an Infant Immunization Program: Increases in Herd Immunity and Replacement Disease

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ABSTRACT

Objectives: In 2003, British Columbia (BC) introduced a universal heptavalent pneumococcal conjugate vaccine (PCV-7) program for infants, and in 2007 revised the recommended schedule from four doses to three doses. We describe trends in the incidence of invasive pneumococcal disease (IPD) in association with these program changes.

Methods: All confirmed cases are reported to the BC Centre for Disease Control (BCCDC) using a standardized data collection process; isolates are forwarded to the BCCDC Public Health and Reference Microbiology Laboratory for serotyping and to the National Reference Laboratory for confirmation. Upon implementation of the reduced dose program in 2007, additional epidemiological data, including immunization history, were collected for children ≤ 16 years.

Results: Seven years after implementation of the program, a 78% decline in incidence of IPD among children under five has been achieved; this is largely a direct effect of the PCV-7 program. Among those >16 years of age, herd immunity is evident and decreasing trends of PCV-7 serotypes continued even after the dose reduction program was introduced. However, gains in disease reduction were offset by increases in replacement serotypes, particularly among the over-65 age group. This has resulted in no net change in adult IPD rates.

Conclusions: The implementation of the PCV-7 program has changed the epidemiology of IPD in BC through direct effects of the vaccine, herd immunity and serotype replacement. The introduction of a three-dose schedule was not associated with an excess of vaccine failures.

Key words: *Streptococcus pneumoniae*; pneumococcal vaccines; population surveillance; immunization schedule

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

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Invasive pneumococcal disease (IPD) is an important cause of bacteremia and meningitis in Canada.¹ In 2003, British Columbia (BC) implemented publicly-funded immunization for infants and young children in order to reduce the burden of illness associated with *Streptococcus pneumoniae*. The 7-valent conjugate pneumococcal vaccine (PCV-7) protects against serotypes 4, 6B, 9V, 14, 18C, 19F and 23F.

BC's Pneumococcal Immunization Program

The PCV-7 program began in April 2003 when a four-dose schedule (at 2, 4 and 6 months with a booster at 18 months) was offered to medically high-risk and Aboriginal children aged 2 to 59 months. In September 2003, the program was expanded to include all infants.

In 2007, BC implemented a schedule change reducing the number of recommended doses of PCV-7 for 'healthy infants' from four to three doses (at 2 and 4 months with a booster at 12 months). This decision was based on published comparative immunogenicity studies and on observations of large numbers of children in the US who only received three doses of the vaccine.²⁻⁴ Medically high-risk children remained on the four-dose schedule, receiving an extra dose at 6 months with the booster dose at 12 months. On June 1, 2010, BC made a program product change from PCV-7 to PCV-13. In addition to the serotypes previously covered by PCV-7, the 13-valent vaccine provides protection against serotypes 1, 5, 7F, 3, 6A and 19A.

The pneumococcal polysaccharide vaccine (PPV-23) protecting against 23 serotypes of IPD is recommended for adults over 64 years of age; medically high-risk children aged two years and older after completion of the PCV series; and high-risk adults, including homeless and illicit drug using populations.⁵

This paper describes changes in the incidence and serotype distribution of IPD in BC in the seven years following implementation of the childhood PCV-7 immunization program in 2003 and under a reduced dose schedule.

METHODS

IPD is reportable in BC, through passive surveillance, to medical health officers and subsequently to the BC Centre for Disease Control (BCCDC). A case is defined as the isolation of *S. pneumoniae* from a normally sterile site. Health Authorities report confirmed cases along with basic demographic information to the BCCDC. Invasive site isolates are voluntarily and routinely submitted to the BCCDC Public Health and Reference Microbiology Laboratory by

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front-line hospital and community laboratories for serotyping and forwarded to a national reference laboratory for confirmation (National Centre for Streptococcus 2002-April 2010, and National Microbiology Laboratory April to December 2010). Serotyping was performed by the Quellung reaction using pool, group, type and factor commercial antisera (SSI Diagnostica; Statens Serum Institute, Copenhagen, Denmark).^{6,7}

Concurrent with the dose reduction program, the collection of additional data elements including immunization history, hospitalization and outcome was introduced in 2007 for persons ≤ 16 years of age, with the primary objective of detecting a possible increase in the number of vaccine failures associated with the new schedule. Only core data elements (i.e., age, sex, Health Authority) are collected for adult cases >16 years of age. For each case notification received from the Health Authorities, two or more personal identifiers (name, date of birth, personal health number) are used to identify a matching laboratory report; isolates were available for 73-90% of cases reported annually between 2007 and 2010. Cases are also identified through receipt of serotyping results from the National Reference Laboratory in the absence of a case notification. Our study did not ascertain completeness of reporting.

In order to account for cases with a missing isolate, the number of PCV-7/non-PCV-7 cases was estimated by applying the distribution of serotyped cases to the total number of cases meeting the case definition. Incidence rates used BC population estimates for the corresponding year and age group.⁷ Changes in incidence rates over time were evaluated using the Cochran-Armitage test for trend at the 1% and 5% significance levels. Statistical analysis was conducted using SAS version 9.2.

RESULTS

Trends in IPD incidence

Overall rates of IPD incidence (all ages, all serotypes) remained relatively stable between 2002 and 2010, with the exception of 2006-2007 during which time there was a large outbreak of *S. pneumoniae* serotype 5 among indigent and drug-using middle-aged adults in Western Canada.^{8,9}

In 2002, rates were driven by the under-five age group; at that time it was estimated that 80% of these cases could be prevented by immunization. Since the introduction of the PCV-7 program in 2003, rates among children under five have fallen by 78% (from 54.4 per 100,000 in 2002 to 11.6 per 100,000 in 2010). As illustrated in Figure 1, the largest reductions were observed in the first three years post-implementation; rates subsequently stabilized with further decreases in PCV-7 serotypes offset by increases in non-PCV-7 serotypes. No increases in overall incidence were temporally associated with the 2007 implementation of the reduced three-dose schedule.

Trends in the distribution of serotypes

Since implementation of the PCV-7 program, there has been a significant ($p<0.01$) declining trend in the proportion of PCV-7 serotypes among all age groups (under 5, 5-16, 17-64 and over 64 years). This pattern was not altered by the introduction of the three-dose schedule in 2007. As illustrated in Figure 2, rates of PCV-7 serotypes steadily decreased from 5.8 to 0.3 per 100,000 population between 2002 and 2010; rates decreased from 46.8 to 0 cases

Figure 1. IPD incidence by age, British Columbia, 2002-2010

Note: Incidence rates were calculated using population denominators from BC Stats PEOPLE 35 database

reported in 2010 among the under-five population, and from 9.6 to 0.7 cases per 100,000 among persons over 64 years of age.

Over the same time period, there was an increasing trend in disease caused by non-PCV-7 serotypes; these trends persisted when outbreak-associated cases were excluded. Increases disproportionately affected the oldest age group. Rates significantly ($p\leq 0.05$) increased among 5 to 16 year olds (1.3 to 2.1 per 100,000) and more than doubled among the 16 to 64 year olds (1.8 to 4.0 per 100,000) and among persons over 64 years of age (5.8 to 12.6 per 100,000).

Based on the distribution of serotypes between 2007 and 2010, an estimated 71% of cases in the over-64 age group were due to PPV-23 serotypes and 48% to PCV-13 serotypes. Figure 3 illustrates the distribution of serotypes for 2007-2010 (excluding outbreak-associated cases) for all ages. Serotypes 3 (10%), 19A (9%), 22F (8%) and 7F (5%) comprise the greatest proportion of cases. The distribution varied by age; serotype 19A disproportionately contributed to disease in the under-five age group, accounting for 26% of typed isolates.

Among cases of all ages, increases in the proportional contribution of serotypes 19A and 7F have been observed; 19A increased from 1.7 to 14.3% and 7F increased from 2.1 to 6.9% between 2002 and 2010.

Vaccine failures

Vaccine failures were monitored in order to assess possible unintended effects of the reduced dose schedule. A vaccine failure is defined as a case of IPD in an age-eligible child (born after July 1, 2003) caused by a vaccine-preventable serotype and occurring 14 or more days following immunization with a) the second dose in a healthy child under one year of age, b) the third dose in a medically high-risk child under one year of age, c) the booster dose (i.e., third or fourth dose depending on health status) in a child one year of age or older, or d) the first dose when that dose was received after two years of age.

Four vaccine failures were identified among vaccine-eligible children between 2007 and 2010; ages were 19 months to 5 years. Two of the four received four doses of PCV-7 prior to 2007; one case caused by serotype 19F had a metabolic disorder; and one case caused by serotype 4 was healthy. The other two vaccine failures were among children who had completed a three-dose schedule and had disease due to serotype 19F. This number of vaccine failures is consistent with the known four-dose efficacy of PCV-7 of 97.4%

Figure 2. Incidence of IPD PCV-7 serotypes by age, British Columbia, 2002-2010 (Excluding all serotype 5 cases reported in 2006-2007)

* Cochran-Armitage test for trend, 2 sided p-value <0.01

† Cochran-Armitage test for trend, 2 sided p-value <0.05

Note: Rates were calculated by applying the distribution of serotypes to confirmed cases.

Serotype data for 2000 to 2006 were estimated from records of isolates submitted to the National Centre for Streptococcus.

Data from 2007 to 2010 were from the same source, but were linked to confirmed BC cases in the Enhanced Surveillance data set.

Rates were calculated using population estimates obtained from BC Stats, PEOPLE 35 database. 2002-2010.

(82.7-99.9%) and effectiveness of one or more doses of 96% (95% CI 93-98) for PCV-7 serotypes in healthy children.^{2,4} The number of cases among children under five years of age caused by PCV-7 serotypes decreased from an estimated 98 cases in 2002 to no cases in 2010. The aforementioned US case-control study found a lower vaccine effectiveness against serotype 19F of 87% (95% CI 65-95) compared to other PCV-7 serotypes.² There were four additional cases due to PCV-7 serotypes among vaccine-eligible children who were unvaccinated: two were <2 months of age (too young to be immunized) and two were between 4 months and 2 years of age.

There were 94 cases of IPD due to non-PCV-7 serotypes in age-eligible children between 2007 and 2010.

DISCUSSION

Direct effects of immunization

Direct effects of the PCV-7 immunization program are most apparent in the under-five age group among whom a 78% decline in incidence (all serotypes) was achieved between 2002 and 2010. Completion of age-appropriate vaccination by the second birthday in BC was 82.2% in 2006, 81.3% in 2007, and 83.0% in 2010 (based on immunization registry data for the 2006 through 2008 birth cohorts, respectively).¹⁰

Similar trends are reported elsewhere. Compared to pre-vaccine baseline, overall declines of 76% were observed in the US popula-

Figure 3. Distribution of PCV-7 and PCV-13 serotype cases of IPD for all ages, British Columbia, 2007-2010

Note: Cases of serotype 5 reported in 2007 were assumed to be outbreak-related and were excluded.

tion under 5 years of age and declines of 73% in the Alberta population under 2 years of age.^{11,12} The greatest disease reductions occurred in the first two years post-implementation and were attributed to PCV-7 serotypes.

Herd immunity

PCV-7 decreases the carriage in the nasopharynx, thereby reducing the likelihood of transmission of vaccine strains, resulting in herd immunity.¹³ BC's data are consistent with herd immunity, demonstrated by a clear decline in rates of PCV-7 preventable disease among those ≤ 16 years old since 2002. Compared to pre-implementation, the incidence of PCV-7 serotypes decreased 94% (2.7 to 0.1 per 100,000) in the 17-64 age group and 91% (9.6 to 0.7 per 100,000) in persons over 64 years of age. This trend did not change with the introduction of the dose reduction program.

The observed decline in PCV-7 serotypes among persons >64 years is unlikely to be a direct effect of PPV-23 immunization. Coverage among this age group was estimated to be 40.9% for BC in 2006; while BC-specific trends in coverage are not available, national estimates suggest that coverage is decreasing with time.^{14,15}

The indirect effect of PCV-7 immunization among unimmunized has been widely reported. Populations with the highest baseline rates of PCV-7 serotypes, highest coverage and longest interval since program implementation report the greatest protection. The most dramatic declines were observed in the US with reductions in PCV-7 serotypes ranging from 87-94% in adult age groups.¹¹ Calgary Health Region has also reported large declines of 38% and 77% for the 16-64 and 65-84 age groups, respectively.¹⁶ Few European countries have published on herd immunity. Hospitalized persons >65 years of age in Barcelona experienced a 37% reduction in invasive disease due to PCV-7 serotypes.¹⁷ Conversely, the Netherlands reported no evidence of herd immunity two years post-implementation despite high coverage.¹⁸

Replacement disease

PCV immunization has the potential to contribute to the emergence of new serotypes through the replacement of endemic

serotypes.¹⁹ Replacement disease is caused by an increase in the incidence of serotypes not included in the vaccine.

The large outbreak of serotype 5 in the adult drug-using and homeless populations accounting for 50% and 32% of BC cases in 2006 and 2007, respectively, are not suggestive of serotype replacement as few cases of this serotype have been reported in recent years (seven in 2009 and two in 2010). This outbreak occurred in unimmunized populations and was driven by socio-economic factors.^{8,9}

The emergence of replacement serotypes has been widely reported, particularly serotypes 19A, 22F and 7F.¹⁷ In the US, a gradual increase in non-PCV-7 serotypes has been reported since implementation of the PCV-7 program. To date, the reductions in PCV-7 serotypes have more than offset increases in non-PCV-7 serotypes, resulting in an overall decline in IPD incidence.¹¹ Similarly in Calgary Health Region, an increase in non-PCV-7 serotypes of 183% (partly attributed to the serotype 5 outbreak) has been offset by decreases in PCV-7 serotypes, resulting in net benefit. In other populations, a net increase has been observed, such as among hospitalized adult patients in Barcelona where a 40% increase has been seen (95% CI 21-61) and is attributed to replacement serotypes.¹⁷

In BC, increases in replacement serotypes (excluding outbreak-associated cases) have disproportionately affected older adults and offset gains achieved through herd immunity, resulting in no net change in rates in this age group. Small decreases in 2010 rates compared to the previous year may represent an anomaly attributed to very low influenza-like-illness (ILI) rates (below the 10-year 25th percentile for medical service plan claims); epithelial disruption from the influenza virus can facilitate the entry of encapsulated pathogens such as *S. pneumoniae*.²⁰ Also, uptake of public health messaging during the 2009-10 pandemic may have increased uptake of PPV-23, handwashing and personal isolation practices among the public, further limiting transmission.

The emergence and burden of disease caused by replacement serotypes is important to monitor. Given that increases in non-PCV-7 serotypes are disproportionately affecting older adults, if

replacement serotypes cause more severe outcomes than vaccine-preventable disease, a possible unintended outcome of the PCV program is a shift in the burden of disease from children to the elderly. A limitation of BC's surveillance data is the ability to detect this type of change; additional epidemiological variables were only collected for children and youth aged ≤ 16 years starting in 2007; these variables (e.g., immunization status or morbidity indicators) were not collected for adult cases. As 71% of cases > 64 years of age reported between 2007 and 2010 were caused by serotypes in PPV-23, this publicly funded vaccine may be underutilized and warrants additional promotional efforts.

CONCLUSIONS

The PCV program has dramatically reduced IPD among children under five years of age. Significant declining trends in PCV-7 preventable disease were associated with direct effects of the vaccine and herd immunity. The three-dose schedule was not associated with an excess of vaccine failures. Adults have benefited from herd immunity, however, anticipated overall disease reduction among adults has not been realized due to a concurrent increase in replacement serotypes. Collection of relevant epidemiological variables including immunization status and morbidity indicators among all age groups is necessary to detect further changes in the epidemiology and preventability of cases anticipated with the recent implementation of the PCV-13 program to help guide further prevention efforts.

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RÉSUMÉ

Objectifs : En 2003, la Colombie-Britannique (C.-B.) a instauré un programme de vaccination antipneumococcique universelle des nourrissons par le vaccin conjugué heptavalent (PCV7), et en 2007, la province a réduit de quatre à trois le nombre de doses recommandées dans le calendrier de vaccination. Nous décrivons les tendances de l'incidence des maladies invasives à pneumocoque (MIP) associées à cette modification du programme.

Méthode : Tous les cas confirmés sont déclarés au BC Centre for Disease Control (BCCDC) selon un processus standardisé de collecte de données; les isolats sont transmis au laboratoire de santé publique et de référence en microbiologie du BCCDC pour sérotypie et au laboratoire de référence national pour confirmation. Lorsqu'on a instauré le programme à doses réduites en 2007, des données épidémiologiques supplémentaires, dont les antécédents vaccinaux, ont été recueillies pour les enfants de 16 ans et moins.

Résultats : Sept ans après la mise en œuvre du programme, l'incidence des MIP chez les enfants de moins de cinq ans a baissé de 78 %; c'est dans une large mesure un effet direct du programme PCV7. Chez les moins de 16 ans, l'immunité collective est manifeste, et la tendance baissière des sérotypes avec le PCV7 s'est maintenue même après l'instauration du programme à doses réduites. Cependant, les gains obtenus au chapitre de la diminution de la maladie ont été compensés par la hausse des sérotypes de remplacement, particulièrement chez les plus de 65 ans. Il n'y a donc eu aucun changement net dans les taux de MIP chez les adultes.

Conclusion : La mise en œuvre du programme PCV7 a modifié de trois façons l'épidémiologie des MIP en C.-B. : par l'effet direct du vaccin, l'immunité collective et le remplacement des sérotypes. L'instauration du calendrier de vaccination en trois doses n'était pas associée à un surcroît d'échecs vaccinaux.

Mots clés : streptococcus pneumoniae; vaccins antipneumococciques; surveillance de population; calendrier vaccinal