

Pneumococcal conjugate vaccination in Canadian infants and children younger than five years of age: Recommendations and expected benefits

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INTRODUCTION: *Streptococcus pneumoniae* infection may result in invasive pneumococcal disease (IPD), such as bacteraemia, meningitis and bacteremic pneumonia, or in non-IPD, such as pneumonia, sinusitis and otitis media. In June 2001, a heptavalent pneumococcal conjugate vaccine (PCV7) (Prevnar, Wyeth Pharmaceuticals, Canada) was approved for use in children in Canada. The objective of the present paper is to review *S pneumoniae*-induced disease incidence and vaccine recommendations in Canadian infants and children younger than five years of age. Particular attention is given to the expected benefits of vaccination in Canada based on postmarketing data and economic modelling.

METHODS: Searches were performed on PubMed and Web of Science databases and specific Canadian journals using the key words 'pneumococc*', 'vaccine', 'conjugate', 'infant' and 'Canadian'.

RESULTS AND DISCUSSION: PCV7 appears to be safe and effective against IPD and non-IPD in children younger than five years of age and, more importantly, in children younger than two years of age (who are at highest risk for IPD). An examination of postmarketing data showed a reduction in incidence of pneumococcal disease in age groups that were vaccinated and in older age groups, indicating the likelihood of herd protection. Concurrently, there was a reduction in the occurrence of antimicrobial-resistant isolates.

CONCLUSIONS: The results from the present review suggest that PCV7 is currently benefiting Canadian children and society by lowering *S pneumoniae*-associated disease. Additional gains from herd protection and further reductions in antimicrobial resistance will be achieved as more Canadian children younger than five years of age are routinely vaccinated with PCV7.

Key Words: Conjugate; Economic; Infant; Pneumococcus; Post-marketing; Prevnar; Streptococcus pneumoniae

Streptococcus pneumoniae is an important cause of childhood disease in Canada (1). This bacteria commonly colonizes the upper respiratory tract and occasionally spreads into the blood or into neighbouring tissues, resulting in invasive pneumococcal disease (IPD), including bacteraemia, meningitis and bacteremic pneumonia, or non-IPD (NIPD), including pneumonia, sinusitis and otitis media. Groups most commonly

Le vaccin conjugué contre le pneumocoque chez les nourrissons et les enfants canadiens de moins de cinq ans : Les recommandations et les bienfaits prévus

INTRODUCTION : L'infection au *Streptococcus pneumoniae* peut provoquer une maladie invasive à pneumocoque (MIP), telle qu'une bactériémie, une méningite ou une pneumonie bactériémique, ou une maladie non invasive à pneumocoque (MNIP) comme une pneumonie, une sinusite ou une otite moyenne. En juin 2001, l'utilisation d'un vaccin conjugué contre le pneumocoque heptavalent (VCP7) (Prevna, Wyeth Pharmaceutiques, Canada) a été approuvée pour les enfants au Canada. Le présent article vise à analyser l'incidence de maladies induites par le *S pneumoniae* et des recommandations de vacciner chez les nourrissons et les enfants canadiens de moins de cinq ans. On s'intéresse notamment aux bienfaits prévus de la vaccination au Canada d'après des données postcommercialisation et une modélisation économique.

MÉTHODOLOGIE : Des recherches ont été effectuées dans les bases de données PubMed et Web of Sciences de même que dans des magazines canadiens précis, à l'aide des mots clés « pneumococc* », « vaccine », « conjugate », « infant » et « Canadian ».

RÉSULTATS ET DISCUSSION : Le VCP7 semble sûr et efficace contre la MIP et la MNIP chez les enfants de moins de cinq ans et, surtout, chez ceux de moins de deux ans (plus vulnérables à la MIP). Un examen des données postcommercialisation a révélé une diminution de l'incidence de maladie à pneumocoque dans les groupes d'âge vaccinés et dans les groupes plus âgés, ce qui laisse supposer une protection collective. En parallèle, on a constaté une réduction de l'occurrence des isolats résistants aux antimicrobiens.

CONCLUSIONS : D'après les résultats de la présente analyse, le VCP7 serait bénéfique pour les enfants et la société du Canada car il réduirait le nombre de maladies associées au *S pneumoniae*. De plus, l'immunité collective et la diminution supplémentaire de la résistance aux antimicrobiens augmenteront à mesure que le nombre d'enfants canadiens recevant systématiquement le VCP7 s'accroîtra.

affected are elderly people, the immunocompromised, specific ethnic groups and young children, particularly those younger than two years of age (2,3). In Canada, it has been estimated that for children aged six months to nine years, the cumulative risk is one in 5000 for pneumococcal meningitis, one in 500 for pneumococcal bacteraemia and one in 20 for pneumonia caused by pneumococcus (1).

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TABLE 1
Incidence rates of *Streptococcus pneumoniae*-associated diseases for a cohort of Canadian children

S <i>pneumoniae</i> -associated condition	Age group (months)	Incidence rate
Pneumococcal meningitis	6 to 11	19.4/100,000
	12 to 23	4.6/100,000
	24 to 36	1.0/100,000
Pneumococcal bacteremia	6 to 11	94.8/100,000
	12 to 23	78.3/100,000
	24 to 36	32.6/100,000
Hospitalized pneumococcal pneumonia	6 to 11	2.5/1000
	12 to 23	2.0/1000
	24 to 36	1.4/1000
Nonhospitalized pneumococcal pneumonia	6 to 11	7.44/1000
	12 to 23	6.93/1000
	24 to 36	4.51/1000
Pneumococcal acute otitis media	6 to 11	223.9/1000
	12 to 23	175.8/1000
	24 to 36	106.5/1000
Mycrotomy with ventilation tube placement due to pneumococcal infection	6 to 11	5.7/1000
	12 to 23	11.0/1000
	24 to 36	5.9/1000

Data from reference 1

In June 2001, the first pneumococcal conjugate vaccine (PCV) was approved for use in children in Canada. In 2002, the National Advisory Committee on Immunizations (NACI) recommended the use of the heptavalent PCV (PCV7) (Prevair, Wyeth Pharmaceuticals, Canada) in all children younger than two years of age; particular recommendations were also made for children two to five years of age, especially for those at moderate to high risk for IPD (2). As of January 2006, all provinces and territories will have added this vaccine into their routine childhood vaccination programs. The objective of the present paper is to review *S pneumoniae*-induced disease incidence and vaccine recommendations in Canadian infants and children younger than five years of age. Particular attention is given to the expected benefits of vaccination in Canada based on postmarketing data and economic modelling.

METHODS

PubMed and Web of Science databases were searched, as were specific Canadian journals, including *The Canadian Journal of Infectious Diseases and Medical Microbiology* and *The Canadian Journal of Public Health*, for relevant references published after 1995. For the search, 'pneumococci' and 'vaccine' were used as key words. The number of references was then limited by the addition of specific terms ('conjugate', 'infant' and 'Canadian') into the search. Specific references published before 1995 were identified in the reference lists of selected papers, and Web sites were searched for provincial or territorial information. References not selected were mainly practice guidelines and studies of a physiological, immunological or molecular nature. In total, 278 abstracts were reviewed to identify relevant papers for the present review. Of these abstracts, 140 were chosen for complete review based on the latest information pertinent to pneumococcal disease and vaccines in children. There were 19 review articles, 24 epidemiology studies (including incidence and serotype studies), 30 effectiveness studies (including clinical trials, and safety and immunogenicity

studies), seven articles regarding vaccine recommendations, 33 economic studies (including cost-effectiveness studies and the need for and cost of increased vaccine uptake), 20 studies on postmarketing analysis and seven miscellaneous articles (including letters and provincial news releases).

RESULTS AND DISCUSSION

Pneumococcal disease in Canadian children

Incidence of pneumococcal disease in Canadian children: *S pneumoniae* is a leading cause of bacterial disease in Canada. In a Canadian, coast-to-coast retrospective study from 1991 to 1998 (4), 2040 records from cases of IPD in children 18 years of age or younger from 11 pediatric centres were examined for epidemiological trends. Male children were affected more often than female children (1.4:1), and the overall risk of disease decreased with age. Children younger than three years of age accounted for 71% of the total cases (29% were younger than 12 months of age, 32% were between 12 and 23 months of age, and 10% were between 24 and 35 months of age). In a related study (5), the average cumulative risk of IPD in these same cities for children in the first five years of life was determined to be one in 460, with a range of one in 732 in Calgary, Alberta, to one in 271 in Vancouver, British Columbia.

Recently, the incidence rates of *S pneumoniae*-associated disease for a yearly cohort of 340,000 Canadian newborns followed from six months to nine years of age have been estimated using provincial databases, ad hoc surveys and previously published data (Table 1) (1). The risk of IPD is highest in children between six and 12 months of age, but still remains relatively high in all children younger than five years of age. An estimated 15 deaths occur in Canada each year in children younger than five years of age from pneumococcal meningitis, hospitalized bacteremia and hospitalized pneumonia (2).

There are estimated to be over one million cases of acute otitis media (AOM) (approximately 200,000 cases caused by pneumococcus) and 1.8 million physician visits for AOM (approximately 360,000 visits for pneumococcus) for children younger than five years of age in Canada each year. In addition, there are over 20,000 myringotomies with ventilation tube placement (MVT) (not all attributed to pneumococcus) performed each year in these children (1,2).

High-risk groups and risk factors: In addition to young age, there are a number of other risk factors that predispose children to IPD (Table 2) (2). Approximately 25% of children with IPD have an underlying illness.

In addition to immunocompromised patients, other groups at increased risk for IPD include Aboriginals, children with cochlear implants and children who attend daycare (6-9). In the United States (US), certain ethnic groups have an increased risk of disease, including American Indians, Alaska Natives and African Americans (10). Data collected in 2001 from Aboriginals and non-Aboriginals in the northern regions of Canada (11) showed that Aboriginals accounted for 96% of all IPD cases in a population of 127,870. There were 45 cases of IPD out of 75,075 Aboriginal Natives and two cases of IPD out of 52,795 non-Aboriginal Natives. The proportion of Aboriginal and non-Aboriginal children younger than two years of age was eight of 3560 and zero of 1182, respectively. Reasons for the increased risk are likely multifactorial, and may include crowded homes and a low rate of breastfeeding (12). Children who received cochlear implants before six years of age are also at higher risk for

meningitis (7). Between 1997 and mid-2001, the incidence rate (138 cases/100,000 person-years) was greater than 30 times the risk of similarly aged American children in 2000. Associated risk factors included a particular model of cochlear implant and inner ear malformations in conjunction with cerebrospinal fluid leaks. Children who attend group daycare have also been identified to be at increased risk for IPD and AOM (7,8). The increase in risk may be associated with poor hygiene, crowding and increased viral respiratory infections – conditions that support a likely environment for *S pneumoniae* promotion and transfer (13).

Pneumococcal vaccine and recommendations in Canada

PCVs in Canada: In June 2001, PCV7 was approved for use in children in Canada. Previously licensed 23-valent pneumococcal polysaccharide vaccines (PPV23) were shown to be poorly immunogenic in children younger than two years of age and in immunocompromised individuals (14). In PCV, the individual capsular polysaccharides are linked to the carrier protein CRM197, a nontoxic mutant of a diphtheria toxin that stimulates a T cell-dependent response, with subsequent anamnestic response upon re-exposure (15,16).

The seven capsular serotypes that are contained within the vaccine are the most prevalent invasive serotypes in North American children and provides the most protection against IPD in infants and young children (17). PCV7 contains serotypes 4, 6B, 9V, 14, 18C, 19F and 23F. These serotypes correspond with 84% to 95% of the serotypes isolated from IPD in children younger than five years of age throughout Canada (4,18,19). Because serotypes of the same serogroup may produce cross-protection, immunization may result in broader protection than the seven vaccine serotypes (VS) (20). For example, serotype 6B in the vaccine may stimulate protection against serotype 6A in addition to the expected serotype 6B.

Vaccine safety has been reported in clinical trials and from an analysis of two years of data collected by the US Vaccine Adverse Event Reporting System (16,21-23).

Clinical vaccine studies: To date, there have been several unpublished PCV7 immunogenicity and safety studies performed in Canada. Preliminary results reveal that PCV7 is safe and results in strong antibody responses to pneumococcal antigens when given with other routine vaccines that make up the Canadian vaccine schedule. Currently, there are several published trials from the US (northern California and Native American studies) and from Africa (rural Gambia and Soweto, and South Africa) that have evaluated the efficacy of PCV against *S pneumoniae*-associated disease in children (21,24-26). Clinical trials have found a 71% to 94% and 42% to 89% vaccine efficacy in VS and non-VS (NVS) IPD, respectively, in their intent-to-treat groups (21,25,26). Similar reductions in IPD were experienced among a smaller group of low-birth-weight infants (under 2500 g) and preterm infants (younger than 38 weeks of gestation) (27).

Vaccine efficacy for radiographically proven pneumonia was also assessed in three studies (25,26,28) and ranged from 21% to 37% in the per protocol group and from 18% to 35% in the intent-to-treat group. This PCV-induced reduction in radiographically proven pneumonia may only be significant in the first two years of life (28).

The efficacy of PCV7 against AOM and MVT has previously been evaluated (24,29-32). Cases of AOM dropped significantly by 6% to 17% in three clinical trials (24,29,30). Two

TABLE 2
Risk factors that predispose children to invasive pneumococcal disease

Risk	Risk factor
High risk	Sickle cell disease, congenital or acquired asplenia, or splenic dysfunction Infection with HIV
Presumed high risk (attack rate unknown)	Congenital immune deficiency Diseases associated with immunosuppressive therapy or radiation therapy (including malignant neoplasms, leukemias, lymphomas and Hodgkin's disease) and solid organ transplantation Chronic renal insufficiency, including nephrotic syndrome Chronic cardiac disease (particularly cyanotic congenital heart disease and cardiac failure) Chronic pulmonary disease (excluding asthma, except those treated with high-dose oral corticosteroid therapy)
Moderate risk	Cerebrospinal fluid leaks Poorly controlled diabetes mellitus All children 24 to 59 months of age, especially children 24 to 36 months of age, children attending group child care, and children in Aboriginal populations living in northern Canada

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studies have reported that MVT procedures were significantly reduced by 24% and 44% (24,31). Another clinical trial, based in the Netherlands, evaluated the efficacy of PCV7 in combination with PPV23 against AOM in older children (one to seven years of age) and found no benefit of vaccination (32).

Pneumococcal vaccine clinical trials have been conducted in some high-risk children. As mentioned above, Native American children (Navajo and White Mountain Apache) have participated in a clinical trial (21). Vaccine efficacy for VS IPD in HIV-positive children from the Soweto study was 65% ($P<0.05$) (26). In other safety and immunogenicity studies involving high-risk children, PCV was capable of generating anti-VS antibodies and a memory response (22,33,34).

Vaccine recommendations in Canada: Recommendations regarding PCV7 have been published by the Public Health Agency of Canada (formerly Health Canada) (2,35,36). NACI has recommended vaccinating all infants at two, four, six, and 12 to 15 months of age. Provincial schedules vary in the time of the fourth or final booster. Many provinces have the final booster to be given at 18 months of age (37). NACI recommends that infants should not be vaccinated before six weeks of age, and that vaccines should be given approximately eight weeks apart with no less than four weeks in between vaccines. If the first vaccine occurs between seven to 11 months, then only the last three doses should be given. If the first vaccine occurs between 12 to 23 months, then only the last two doses should be given, eight weeks apart. Premature babies should be vaccinated similarly, at their birth age.

Specific recommendations for moderate- and high-risk children younger than five years of age have also been made by the NACI. High-risk children include children with sickle cell disease, anatomical or functional asplenia, and HIV, as well as

those conditions listed in Table 2. If high-risk children are not vaccinated before two years of age, then two PCV7 vaccines followed by one PPV23 vaccine should be given at least eight weeks apart. If the recommended PCV7 protocol is complete before two years of age, then a PPV23 booster should be given at least eight weeks after the last PCV7 vaccine was given.

A PPV23 booster increases the spectrum of serotypes and increases the immune response (2,3). A PPV23 booster is also recommended for Aboriginal children after recommended vaccination with PCV7. The common serotypes isolated in IPD in northern Canadian Aboriginals include serotype 1 (11), which is not contained in PCV7. PPV23 is a fundamental component of pneumococcal vaccination in high-risk children and should not be overlooked in light of new provincial and territorial PCV7 programs.

Other moderate-risk children that should be considered for PCV7 vaccination are group daycare attendees between 24 and 35 months of age. Although PPV23 is immunogenic in children older than two years of age, PCV7 is recommended for healthy children between 24 and 59 months of age because of induction of the immune response and expected higher efficacy against VS IPD and NIPD, including AOM.

For specific, recommended vaccination schedules for healthy and high-risk children, publications from the Public Health Agency of Canada should be consulted (2,35-37). Particular recommendations are available if there is an interruption in the vaccine schedule (35).

Hypothesized PCV7 benefits in Canada

Provincial funding for PCV7 vaccination in Canada has been increasing since licensing in 2001. Extensive postmarketing data analysis is available in the US; however, it is not yet available in Canada. The incidence of IPD in Canadian children younger than two years of age is slightly lower than the incidence in the US, but this discrepancy may actually be due to less frequent blood culturing for febrile illness in Canada and, therefore, fewer cases of pneumococcal bacteremia being detected (1,5,38). PCV7 covers a similarly high proportion of Canadian and American *S pneumoniae* isolates (24). Because of the similarities between pneumococcal disease in Canada and the US, the expected health benefits from vaccination in Canada can be extrapolated from published US data. Although there is some published US postmarketing information on specific results of PCV vaccination, such as herd protection, effects on antimicrobial resistance (AMR) and serotype replacement, the potential of these vaccination results in Canada will also be illustrated by particular clinical trials.

PCV7 postmarketing reduction in pneumococcal disease: In February 2000, the PCV7 vaccine was licensed in the US for routine immunization of infants and young children. Since the introduction of the vaccine, many state and multiregional studies have shown a dramatic decline in IPD in young children (39-44). Among eight children's hospitals, the rate of IPD in children younger than 24 months of age dropped by 58% in 2001 and 66% in 2002 when compared with the average rate from 1994 to 2000 (43). VS IPD dropped by 63% in 2001 and 77% in 2002. A multistate study (44) found a 69% ($P<0.001$) and 78% ($P<0.001$) reduction in all-cause IPD and VS IPD, respectively, in children younger than two years of age for the year 2001 (compared with the mean rate for 1998 and 1999). A recent study by the US Centers for

Disease Control and Prevention (45) found that the rate continues to decline, with a 94% reduction in VS-specific IPD in children under two years of age for the year 2003 compared with 1998 and 1999. In addition to the dramatic reduction in IPD, racial disparities in the risk of IPD in African Americans and Caucasians have been reduced considerably since the introduction of PCV7 (46,47).

Reductions in AOM and MVT have also been experienced (48). Poehling et al (39) reported a 6% reduction in all AOM cases in Tennessee and a 20% decrease in AOM in upstate New York in 2001/2002.

Preliminary results from an ongoing pneumococcal disease and serotype surveillance study in Calgary (Calgary Area *Streptococcus pneumoniae* Epidemiology Research [CAPSER], run by Dr J Kellner) suggest that the vaccine should perform similarly in Canada as it has in the US. These preliminary results have shown a 62% decrease in VS and vaccine-related serotype IPD incidence in children between six and 23 months of age in 2003 compared with the average incidence between 1998 and 2001 (personal communication, Dr J Kellner). By 2004, the incidence had decreased by 93% compared with the average incidence between 1998 and 2001 in Calgary (49).

Outcome of vaccination on herd effect: A potential indirect effect of vaccination is the reduction of disease in nonvaccinees, otherwise known as herd protection (50). Evidence (14) suggests that herd protection to pneumococcal disease occurs from reduced nasal carriage of VS following vaccination, resulting in reduced transmission and spread of the pathogen. The reduction in VS nasal carriage after PCV vaccination has been observed in many studies, including those performed on PCV-vaccinated daycare attendees versus controls (13,15,51-54). Herd protection was also demonstrated by the decrease in nasal carriage in the nonenrolled siblings of the vaccinated daycare attendees (13).

According to the US postmarketing data, reductions in IPD were experienced among adults, suggesting a reduction in *S pneumoniae* transmission to unvaccinated people from vaccinated children (44,46). The rate of IPD in 2001 dropped significantly ($P<0.05$) by 32% in adults 20 to 39 years of age, by 8% in adults 40 to 64 years of age, and by 18% in adults 65 years of age or older when compared with rates in 1998 and 1999.

The effects of herd protection in Canada should result in similar reductions of pneumococcal diseases in children and all other age groups by reducing transmission and spread of pneumococcus.

Effect of vaccination on AMR: Another potential effect of pneumococcal vaccination is a reduction in antimicrobial-resistant *S pneumoniae*. Long-term follow-up of the Northern California clinical trial (55) has demonstrated a reduction in isolates that are highly resistant to penicillin recovered from IPD in young children, from 15% in 2000 (at the start of routine vaccination) to 5% in the first half of 2003. Multiregional US postmarketing data analysis has shown a significant decrease in the proportion of penicillin-resistant IPD isolates, from a peak of 45% in 2001 down to 33% in 2002 ($P=0.018$) (43).

It is believed that vaccination with multivalent PCV reduces the rate of AMR isolates by two primary mechanisms. First, the vast majority of pneumococcal isolates resistant to penicillin, cefotaxime, trimethoprim-sulfamethoxazole and multiple drugs are of the serotypes 6A, 6B, 9V, 14, 19F, 19A

and 23F (15,50,56). These are the PCV7 serotypes or related serotypes and, therefore, vaccination would lead to a reduction of the nasal carriage or spread of these resistant isolates. Second, vaccination decreases the frequency of pneumococcal disease, leading to reduced antibiotic usage and antibiotic pressure on the isolates. Reduction of antibiotic-resistant *S pneumoniae* carriage has been demonstrated in PCV-vaccinated daycare attendees (15). In another study (29), vaccinated children had an overall 17% reduction in antibiotic usage days.

As for antibiotic-resistant pneumococcal isolates found in Canada, different studies have reported the proportions of penicillin-resistant isolates that would have been covered by the serotypes in PCV7 (4,18,19,57). These proportions included 94% in children younger than two years of age, 95% in children 18 years of age or younger, and 100% in the general population. The CASPER surveillance preliminary data analysis showed that in 2003, the proportion of pneumococcus IPD isolates not susceptible to penicillin in children younger than 16 years of age decreased from previous years (personal communication, Dr J Kellner). Thus, it is expected that the routine vaccination of Canadian children will have a significant impact on reducing the rates of antibiotic-resistant pneumococcus in Canada.

Effect of vaccination on serotype replacement: One potential consequence of vaccination is the exchange of the target pathogen with replacement pathogens. With respect to *S pneumoniae*, there is limited evidence to suggest that vaccination may result in increased nasal colonization by NVS (15,32,51). A follow-up to the large-scale Northern California clinical trial (55) found no significant increase in the rate of NVS IPD in children younger than five years of age. In the Finnish AOM study, however, there was a 33% increase in the number of cases of AOM caused by NVS in vaccinated children younger than two years of age compared with control subjects (30). Similarly, in a US postmarketing study (43), a small increase in IPD cases caused by NVS was identified, particularly in serogroups 15 and 33. The long-term impact of *S pneumoniae* serotype replacement on *S pneumoniae* epidemiology in Canada remains to be seen.

Societal benefits

In addition to reduced morbidity and mortality, routine vaccination of children will be economically beneficial to Canadians.

Direct and indirect cost effectiveness analyses of universal *S pneumoniae* vaccination: Because the investment for vaccine purchase is high at \$67.50/dose (58), the economic benefits of the vaccine need to be high to make this vaccine financially viable for society. Many countries, including Canada, have undertaken economic analyses of universal vaccination (59-68). The studies from North America are summarized in Table 3.

Overall, these studies found varying degrees of both positive and negative cost-effectiveness for routine vaccination of infants (59-68). However, many of the authors of these studies considered the evaluations to be conservative for a variety of different reasons, including conservative estimates of disease incidence, exclusion of pneumococcal disease conditions such as sinusitis and endocarditis, and no account for protection from NVS, indirect benefits (including herd protection) or reduction of AMR (60,61,64,66).

TABLE 3
Summary of heptavalent pneumococcal conjugate vaccine cost-effectiveness studies for children younger than two years of age in North America

Country	Lead author (reference)	Date published	Vaccine cost/dose	Vaccine cost for society to break even*	Societal cost per LYG
US	Lieu (71)	2000	US\$58	US\$46	US\$80,000
Canada	De Wals (66)	2003	CDN\$58	CDN\$30	CDN\$125,000
Canada	Lebel (67)	2003	CDN\$67.50	CDN\$50	CDN\$78,000
Canada	Moore (68)	2003 (British Columbia)	CDN\$67.50	N/A	CDN\$42,000 to \$91,000

*Costs account for direct costs and societal costs of disease, not indirect costs from herd immunity or reduction of antimicrobial resistance. LYG Life-year gained; N/A Not applicable; US United States

Adjusting for these factors can change the estimate from potentially too costly to cost-saving. The indirect benefit of herd protection was accounted for in the sensitivity analysis of one economic model (59). Using herd protection levels identified by Whitney et al (44) for all pneumococcal disease and for only IPD, the cost per quality-adjusted life-years was estimated at £5013 and £18,625, respectively (59). These estimates are much below the base estimate of £59,945.

Canadian, projected, universal *S pneumoniae* vaccination cost-effectiveness: Two Canada-wide economic studies (66,67) have evaluated direct medical and direct nonmedical costs to estimate the cost of disease to the health care payer (66,67). In addition, indirect costs were calculated to estimate the additional cost to society for lost productivity due to illness or death (69). The societal cost per life-year gained was \$78,778 and \$125,000 according to studies by Lebel et al (67) and De Wals et al (66), respectively. Furthermore, the societal vaccine break-even prices were \$50 (67) and \$30 (66), both of which were less than the cost of the vaccine. Differences in costs between the two studies were mainly due to the differences in estimated IPD incidence and vaccine efficacy (69).

Both Canadian studies (66,67) did not account for probable benefits of vaccination resulting from herd protection. In a recent publication (70), estimates from the Lebel et al (67) study were adjusted to account for the herd effect. Using the herd protection estimates of Whitney et al (44), a direct cost savings of \$40.2 million was estimated from the 8531 pneumococcal cases avoided (70). If these savings were added to the original societal savings of \$66.6 million, then the overall societal savings for vaccinating the birth cohort would be \$106.8 million. If the cost of vaccinating (\$91.8 million) was subtracted from the savings from routine pneumococcal vaccination of infants, then the net Canadian societal savings would be \$15 million.

In addition to routine infant pneumococcal vaccinations, some studies have attempted to evaluate the economic effectiveness of catch-up vaccination in children from seven months to five years of age (59,60,64,66,67,71). Lebel et al (67) found catch-up vaccination in all age groups (seven to 11 months, 12 to 23 months and 24 to 60 months of age) to be more cost-effective than the routine vaccination of infants younger than seven months of age and, in general, found it to be cost-effective for society but not the health care payer (67). In contrast, De Wals et al (66) found catch-up vaccination in the same groups to be less cost-effective than the routine vaccination

program and, in general, not cost-effective for society or the health care payer.

The results of the present review suggest that routine infant vaccination with PCV7 is likely cost-saving when all direct and indirect costs (including herd protection and reduction of AMR) are considered. Of course, the cost of suffering from the associated diseases is difficult to quantify and is not included in the economic analyses; however, its importance should not be ignored. As countries continue to adopt national pneumococcal immunization protocols, vaccine prices decline and post-vaccination surveillance of disease incidence continues, new economic evaluations may elucidate the actual societal and health care economic value of PCV7.

CONCLUSION

In June 2001, PCV7 was approved for use in children in Canada. With continued vaccination and surveillance in Canada, the impact of PCV7 on *S pneumoniae*-associated diseases will become more apparent. In addition, further research is necessary to answer important questions relating to optimal vaccination schedules, serotype replacement, AMR, herd protection, length of immunity and actual cost savings.

In summary, PCV7 appears to be safe and effective against IPD and NIPD, including pneumonia and AOM in children younger than five years of age, but more importantly in children younger than two years of age who are at highest risk for IPD. Since the introduction of routine vaccination in the US, there has been a reduction in the incidence of pneumococcal disease

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in age groups that were vaccinated and in older age groups, indicating the likelihood of herd protection. Concurrently, there has been a reduction in the occurrence of AMR isolates, which is likely due to vaccination because most resistant isolates are of the PCV7 serotypes or related serotypes. Finally, if societal costs are added into economic models along with benefits from herd protection and reduction of AMR, then the projected cost savings of routine PCV7 vaccination is expected to be positive.

As of January 2006, all provincial and territorial governments will fund programs for routine immunization of children with PCV7. In addition, some provinces and territories are or will be funding catch-up vaccinations. Catch-up vaccinations are for PCV7-unvaccinated children younger than two years of age or younger than five years of age, depending on the province or territory. The results of the present review strongly suggest that PCV7 is currently benefiting Canadian children and society as a whole by lowering *S pneumoniae*-associated disease. Our results also suggest that additional gains from herd protection and reductions in AMR will be achieved as more Canadian children younger than five years of age are routinely vaccinated with PCV7.

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