Epidemiological and economic burden of pneumococcal diseases in Canadian children

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BACKGROUND: With the arrival of a new conjugate pneumococcal vaccine, it is important to estimate the burden of pneumococcal diseases in Canadian children. The epidemiological data and the economic cost of these diseases are crucial elements in evaluating the relevance of a vaccination program.

METHODS: Using provincial databases, ad hoc surveys and published data, age-specific incidence rates of pneumococcal infections were estimated in a cohort of 340,000 children between six months and nine years of age. The costs of these diseases to the health system and to families were also evaluated using data from Quebec and Manitoba.

RESULTS: Cumulative risks were one in 5000 for pneumococcal meningitis, one in 500 for bacteremia and one in 20 for pneumonia, leading to 16 deaths in the cohort. About 262,000 otitis media episodes and 32,000 cases of myringotomy with ventilation tube insertion were attributable to *Streptococcus pneumoniae*. Societal costs were estimated at $125 million, of which 32% was borne by the health system and 68% was borne by families. Invasive infections represented only 2% of total costs, while 84% were generated by otitis media.

CONCLUSION: Pneumococcal infections represent a significant burden for Canadian children and society that could be significantly reduced through immunization.

Key Words: *Canada; Economics; Epidemiology; Pneumococcal infections*

Fardeau épidémiologique et économique des maladies pneumococciques chez les enfants canadiens.

CONTEXTE : Avec l'arrivée d'un nouveau vaccin pneumococcique conjugué, il est important de mesurer le fardeau des maladies pneumococciques chez les enfants canadiens. Les données épidémiologiques et les coûts économiques de ces maladies sont des éléments cruciaux pour évaluer la pertinence d'un programme de vaccination.

MÉTHODES : À l'aide de bases de données provinciales, de recherches spéciales et de données publiées, on a mesuré les taux d'incidence par âge des infections pneumococciques dans une cohorte de 340 000 enfants âgés de six mois à neuf ans. On a également évalué les coûts de ces maladies pour le système de santé et les familles à l'aide de données du Québec et du Manitoba.

RÉSULTATS : Les risques cumulatifs s'établissaient à un cas sur 5000 pour la méningite pneumococcique, un cas sur 500 pour la bactériémie et un cas sur 20 pour la pneumonie, ce qui s'est traduit par 16 décès dans la cohorte. Environ 262 000 épisodes d'otite moyenne et 32 000 cas de myringotomie accompagnée de l'insertion d'une sonde de ventilation étaient attribuables à une infection à Streptococcus pneumoniae. On a estimé que les coûts sociétaux s'établissaient à 125 millions de dollars, dont 32 % étaient à la charge du système de santé et 68 % à la charge des familles. Les infections invasives représentaient seulement 2 % des coûts totaux, comparativement à 84 % pour l'otite moyenne.

CONCLUSION : Les infections pneumococciques représentent un fardeau important pour les enfants et la société au Canada, lequel on pourrait réduire considérablement grâce à l'immunisation.

Streptococcus pneumoniae is an important cause of serious illness in young children in developed countries (1). A 7-valent pneumococcal conjugate vaccine (PCV-7) has recently been licensed in Canada. This vaccine is now being used in publicly funded programs for all children in Alberta and Nunavut. Some Canadian provinces (Quebec, Prince Edward Island and Saskatchewan) have implemented programs limited to some high-risk groups and others are still considering its use in their provincial programs (2,3). Evaluation of the epidemiological and economic burden of pneumococcal disease is an important criterion in decision making and is a prerequisite for the analysis of the cost-effectiveness of routine and catch-up immunization programs. Epidemiological data collected in the United States may not be valid for Canada because of possible differences in the prevalence of risk factors. Extrapolation is even more problematic for economic parameters because of variations in the composition of families, availability of natural caregivers, employment rates, incomes and costs of health services. The aim of this study is to estimate the incidence and societal costs of pneumococcal disease in Canadian children between six months and nine years of age.

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MATERIALS AND METHODS

The study was based on the estimated yearly cohort of 340,000 Canadian newborns followed from the age of six months to nine years. In a routine immunization program, the primary vaccination series of three doses of PCV-7 are completed by the age of six months; however, there are no solid data on the protection provided by the first and second doses (2). Pneumococcal-related outcomes were selected because of the proven efficacy of PCV-7 for prevention of pneumococcal diseases in clinical trials (4-6). Mutually exclusive outcomes included pneumococcal meningitis and pneumococcal bacteremia with or without pneumonia (cases for these two conditions were identified by isolation of *S pneumoniae* in normally sterile sites), pneumonia with no bacteremia, acute otitis media (AOM) and myringotomy with ventilation tube insertion (MVT). All financial costs were expressed in Canadian dollars (year 2000 rate). To handle inflation, all prices before 1998 were adjusted using the Canadian price index for health and personal care (7).

To estimate the incidence of pneumococcal invasive disease in the province of Quebec, data from three different sources were used: the Provincial Notifiable Diseases Database, the Provincial Reference Laboratory (collects pneumococcal isolates from 26 sentinel hospitals), and the Immunization Monitoring Program Active (a program operated in tertiary care paediatric hospitals including Ste-Justine, the Montreal Children's Hospital and the University Hospital Centre in Quebec City). Cases of invasive pneumococcal disease occurring in patients aged six months to nine years of age during the period from January 1, 1997 to December 31, 1998 were identified and double records were eliminated using variables pertaining to personal characteristics.

Population-based data on invasive pneumococcal disease were also obtained from the Toronto Invasive Bacterial Disease Network (Allison McGeer, written communication), the Calgary Regional Health Authority (James Kellner, written communication), Vancouver area (David Scheifele, written communication), and the (Canadian) Sentinel Health Units Surveillance System (Theresa Tam, written communication). A breakdown of cases by diagnostic category (meningitis and bacteremia) and single-year age groups was provided by the Toronto Invasive Bacterial Disease Network and the Sentinel Health Units Surveillance System, and rates from these two studies were combined with those from Quebec. Combinations of these incidence rates were performed according to a method for meta-analysis for incidence studies described by Cucherat (8) using a weighting factor proportional to the denominator (Table 1). Bacteremia was divided into hospitalized and nonhospitalized types using the proportion observed in the Quebec study (62% of bacteremia cases were hospitalized).

For hospitalized pneumonia, the primary data source was the hospital administrative data system covering all admissions in acute care services in the province of Quebec (MÉD-ÉCHO). Hospital admissions in 1997 and 1998 of infants aged six months to nine years with a main or secondary diagnosis of pneumonia (ICD-9 codes: 480.0 to 487.0) were retrieved. To avoid overlaps with invasive diseases, cases of pneumonia associated with pneumococcal meningitis (ICD-9 code: 320.1) or bacteremia (ICD-9 code: 038.2) were excluded.

The Manitoba Health Administrative Database was used to estimate the incidence of nonhospitalized pneumonia. Medical hospital outpatient and office visit claims from all physicians in the calendar years of 1989 through 1998 with a code of pneumonia (ICD-9 codes: 480.0 to 487.0) were identified. The frequency of claims was converted into a frequency of pneumonia episodes using the average number of medical visits (n=2.2) recorded in our retrospective study of cases of pneumonia in children younger than 10 years of age in Quebec and Manitoba (from the microcosting study of otitis and pneumonia described later). The proportion of pneumonia attributable to *S pneumoniae* was set at 22% based on values found in published studies (9-16).

The Manitoba Health Administrative Database's data on physicians' claims were used to estimate the frequency of age-specific visit rates for AOM (ICD-9 codes: 381 and 382). The average number of medical visits was 1.8 in the retrospective study of nonhospitalized AOM cases in Quebec and Manitoba, and age-specific frequencies of visits were divided by this number to estimate the incidence of AOM episodes. The proportion of AOM attributable to *S pneumoniae* was estimated at 19%, according to literature data and published expert opinions (6,17).

Data on the frequency of MVT was extracted from the MÉD-ÉCHO system for one-day surgery in Quebec for the period of 1997 to 1998. An additional number of MVT cases were found in the short-term hospital stay MÉD-ÉCHO database. Ear, nose and throat specialists in Quebec were consulted and they estimated that about 10% of all MVTs are currently performed in nonhospital settings and exclusively in children five years of age or older. The frequency of MVT in children five years and over was adjusted to take this factor into account.

TABLE 1
Age-specific incidence rate of pneumococcal-related outcomes in a cohort of Canadian children

	Person-years	6 months to 1 year	1 year	2 years	3 years	4 years	5 years	6 years	7 years	8 years	9 years
Pneumococcal meningitis	per 100 000	19.37	4.58	0.99	0.73	0.47	0.46	0.46	0.46	0.46	0.46
Pneumococcal bacteremia	per 100 000	94.81	78.32	32.62	18.53	12.82	4.65	4.65	4.65	4.65	4.65
Hospitalized pneumonia (all causes)	per 1000	11.15	9.25	6.16	4.27	2.91	3.07	2.11	1.61	1.19	0.75
Hospitalized pneumococcal pneumonia	per 1000	2.45	2.04	1.36	0.94	0.64	0.68	0.46	0.35	0.26	0.17
Non-hospitalized pneumonia (all causes)	per 1000	33.80	31.50	26.20	23.00	20.50	18.90	18.80	15.60	13.80	11.80
Non-hospitalized pneumococcal pneumonia	per 1000	7.44	6.93	5.76	5.06	4.51	4.16	4.14	3.43	3.04	2.60
AOM (all causes)	per 1000	1178.60	925.10	560.50	449.00	390.80	356.40	289.80	220.10	170.00	138.50
Pneumococcal AOM	per 1000	223.93	175.77	106.50	85.31	74.25	67.72	55.06	41.82	32.30	26.32
MVT (all causes)	per 1000	11.35	21.89	11.79	10.19	10.06	10.52	9.20	5.98	3.67	2.20
Pneumococcal MVT	per 1000	5.68	10.95	5.90	5.10	5.03	5.26	4.60	2.99	1.84	1.10

AOM Acute otitis media; MVT Myringotomy with ventilation tube insertion. Assuming 22% of all cases of pneumonia, 19% of all cases of acute otitis media, and 50% of all cases of myringotomy with ventilation tube insertion are attributable to S pneumoniae

Case fatality rates for pneumococcal meningitis (6.5%) and hospitalized bacteremia (2.0%) were estimated from the Immunization Monitoring Program Active study (18). The case fatality rate for hospitalized pneumonia was estimated to be one per 1000 (19). It was assumed that no fatal cases occurred in nonhospitalized bacteremia and pneumonia. The proportions of survivors of pneumococcal meningitis with deafness (13%) and neurological disability (7%) were obtained from published studies (20,21). Life years lost were calculated using Canadian life expectancy tables (22).

Estimates of hospital costs were calculated using the All Patient Refined-Diagnosis Related Groups and Resource Intensity Weights classification systems in Quebec. Hospital records of patients with pneumococcal meningitis (ICD-9 code: 320.1), pneumococcal septicemia (ICD-9 code: 038.2), and pneumonia (all causes) (ICD-9 codes: 480.0 to 487.0) were identified, and mean values of the distribution of hospital costs were calculated. Physician fees were calculated with the median length of stay in pediatric and intensive care units for the different diagnostics using the fee specific to service category, assuming that hospitalized children were seen by a pediatrician each day and adding one follow-up visit (23). For meningitis, an additional 10% of the overall cost was added to cover follow-up assessment.

Direct and indirect costs to families were evaluated in a sample of parents whose children had been hospitalized for invasive pneumococcal infection. Parents of 16 patients aged six months to nine years hospitalized at the Sherbrooke University Hospital in the 1998 to 2000 period completed a postal questionnaire designed to evaluate resource use. A cost per unit of resource was assigned to each item, including travel, parking, additional babysitting, and the time family members spent taking care of their sick children. The values of the different cost elements were estimated from different sources. If the parent had lost time from work and if that time could not be replaced, the national mean hourly wage was attributed to these lost hours. The time the family member spent as a volunteer (unpaid) or the time taken from work which could later be replaced was valued with the minimum hourly wage in Quebec ($6.90). Costs of treatments not assumed by the health system are principally the cost of antibiotic treatment in outpatients following hospitalization. This information was assessed from hospital records. It was assumed that costs to families were similar for invasive and noninvasive pneumococcal pneumonia.

A retrospective study was conducted in the summer of 2000 with a sample of 13 physicians from Manitoba and nine from Quebec, including family doctors, pediatricians and physicians working in emergency departments. Participating physicians were invited to provide five cases of nonhospitalized AOM (all causes) diagnosed in the last three months and five cases of pneumonia (all causes) diagnosed in the last 12 months. Eligible cases were children aged between six months and nine years with no underlying medical condition. The study sample was 108 for AOM and 54 for pneumonia. For each case, the physician provided written information on the number of visits, referral to specialists, diagnostic tests and prescribed medication. Parents were invited to answer a telephone questionnaire, including questions on medical visits, calls to a health information line, prescribed and over-the-counter medication, travel, parking, lost hours of salaried and unpaid work, and additional babysitting. To reflect the increased severity of pneumococcal otitis and pneumonia, relative to otitis and pneumonia from all causes, mean health care and family costs were increased by 10%, based on expert opinion.

The cost of nonhospitalized bacteremia was estimated according to the cost information obtained for otitis and pneumonia. The health care cost of bacteremia was assumed to be equivalent to the health care cost of pneumonia plus diagnostic tests routinely done in case of hyperthermia: a complete blood count ($5), a urine culture ($12) and a blood culture ($20). The costs incurred by families for bacteremia was assumed to be equivalent to the costs incurred by families for otitis.

Two sources were used for estimating MVT costs. Costs of one-day MVT surgery were first estimated from indexed results of a study in Ontario (24), including physician service costs, direct surgical costs, preoperative assessment, recovery room

TABLE 2
Unitary costs* of pneumococcal-related outcomes in Canada

	To health system	To families	To society
Meningitis	$10,281	$1424	$11,705
Hospitalized bacteremia	$2386	$1424	$3810
Non-hospitalized bacteremia	$122	$262	$384
Hospitalized pneumonia	$1836	$1424	$3260
Non-hospitalized pneumonia	$85	$532	$617
Acute otitis media	$59	$262	$321
Myringotomy with ventilation tube insertion	$527	$126	$653

**Excluding costs of permanent sequelae*

TABLE 3
Unit costs of non-hospitalized otitis and pneumonia by cost category in two Canadian provinces

Cost categories	Nonhospitalized otitis			Nonhospitalized pneumonia		
	Quebec Mean (SD)	Manitoba Mean (SD)	Mean two provinces	Quebec Mean (SD)	Manitoba Mean (SD)	Mean two provinces
Cost to the health system	$52 ($21)	$54 ($29)	$53	$84 ($39)	$71 ($24)	$77
Cost to families (excluding treatment costs and productivity loss)	$11 ($8)	$21 ($37)	$16	$27 ($31)	$24 ($16)	$26
Cost in treatment	$31 ($23)	$18 ($12)	$24	$62 ($46)	$23 ($18)	$42
Cost in productivity loss (work or voluntary time)	$195 ($234)	$201 ($460)	$198	$468 ($764)	$362 ($402)	$415
Total	$289 ($241)	$295 ($506)	$292	$640 ($809)	$480 ($409)	$560
Total plus 10% to reflect increased severity of pneumococcal infections	$317	$ 324	$321	$704	$528	$616

Means were rounded off to closest dollar. SD standard deviation

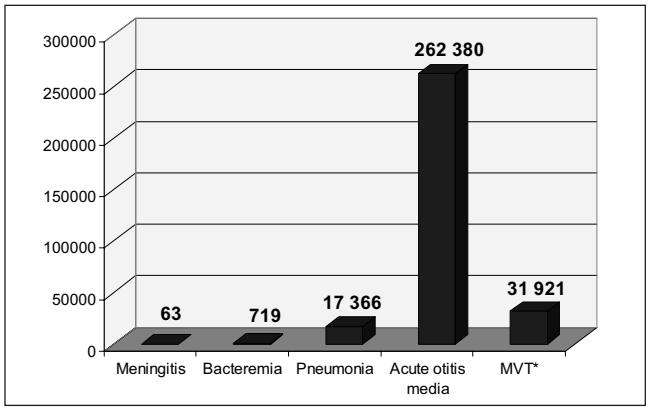

Figure 1) *Number of cases of pneumococcal-related outcomes in a cohort of 340,000 Canadian children between six months and nine years of age. MVT* Myringotomy with ventilation tube insertion*

costs and overhead costs. For surgeries requiring hospitalization, the MÉD-ÉCHO and All Patient Refined-Diagnosis Related Groups database systems in Quebec were consulted, and physician service costs were then added. The health system unit cost of myringotomy was calculated from the weighted average of interventions performed in hospital (including general anesthesia) and nonhospital settings (excluding general anesthesia). Since MVT is an elective surgery, no loss of work was assumed for parents, but a total of 16 h of care time was included in the costs to families, using the minimal hourly wage in Quebec of $6.90. Other costs to families were based on data collected for AOM.

RESULTS

Age-specific incidence rates of selected pneumococcal-related outcomes are presented in Table 1. Disease incidence is highest between six and 12 months and decreases gradually with age. Invasive pneumococcal infections are mostly seen in children under two years of age. AOM is by far the most frequent condition. MVTs are more evenly distributed, but are less frequently performed during school years.

Unitary costs of pneumococcal-related outcomes are presented in Table 2. Hospitalization is a major determinant of costs and the largest share of total costs of meningitis, hospitalized bacteremia and pneumonia are borne by the health system. This is also true for MVT requiring a surgical setting. For nonhospitalized pneumonia and AOM, the burden is mostly on families. Table 3 presents the cost distribution for nonhospitalized AOM and pneumonia.

The epidemiological burden of pneumococcal disease in a cohort of 340,000 Canadian children is shown in Figure 1. The cumulative risk of pneumococcal meningitis between six months and nine years of age was about one in 5000, about one in 500 for pneumococcal bacteremia, and about one in 20 for pneumococcal pneumonia. In the cohort, the total number of AOM attributable to *S pneumoniae* was about 262,000 and approximately 32,000 cases of MVT could be due to this cause. Sixteen deaths were attributable to pneumococcal disease, corresponding to a loss of 1536 life-years (not presented in the figure). In addition, there were 12 patients who survived with permanent physical sequelae from pneumococcal meningitis.

The economic burden associated with pneumococcal disease is presented in Table 4. The overall societal costs of all cases of pneumococcal disease amounted to more than

TABLE 4
Costs* of pneumococcal disease in a cohort of 340,000 Canadian children from six months to nine years of age

	Costs to health system	Costs to families	Costs to society
Meningitis	$649,000	$97,000	$746,000
Hospitalized bacteremia	$1,070,000	$655,000	$1,725,000
Nonhospitalized bacteremia	$34,000	$71,000	$105,000
Hospitalized pneumonia	$5,022,000	$4,108,000	$9,130,000
Nonhospitalized pneumonia	$1,261,000	$7,748,000	$9,009,000
Acute otitis media	$15,148,000	$69,008,000	$84,156,000
Myringotomy with ventilation tube insertion	$16,872,000	$3,958,000	$20,830,000
Total	$40,224,000	$85,477,000	$125,701,000

**Excluding costs of sequelae and productivity losses associated with deaths and disabilities. Assuming 22% of all cases of pneumonia, 19% of all cases of acute otitis media, and 50 % of all cases of myringotomy with ventilation tube insertion are attributable to* S pneumoniae

$125 million and 32% of this was borne by the health system, while 68% was borne by families. Invasive pneumococcal infections represented only a small fraction of the overall disease cost of $2,600,000 or 2% of total costs. A large proportion of invasive disease costs (68%) was borne by the heath system. About 98% of pneumococcal disease costs were generated by noninvasive infections, with AOM and MVT representing 84% of the total. Approximately 69% of noninvasive pneumococcal disease costs were borne by families.

DISCUSSION

This is the first study aiming to estimate the epidemiological and economic burden of pneumococcal disease in Canadian children. The analysis was restricted to pneumococcal meningitis, bacteremia, pneumonia, and otitis. Other infections, such as sinusitis, bronchitis, arthritis and other rare infections were not included because there are no data regarding PCV-7 efficacy against these infections (4-6). Long-term healthcare costs and productivity losses associated with neurological disability and permanent hearing loss were not estimated for lack of precise data. Pain, sorrow, anxiety and interpersonal tensions caused by pneumococcal disease were not assigned values because psychological costs have not been standardized as utilities in population-based studies (25). Thus, estimates of the burden of pneumococcal disease in this study are conservative.

Incidence rates of invasive pneumococcal infections measured in the present study are lower than those reported in the white American population, especially among young children (26). As expressed by Bjornson et al (27), variations in the frequency of blood cultures in pediatric cases of febrile disease are a plausible explanation, although true variation of disease due to variations in risk factors is also possible (eg, smoking or day care centre attendance). In Canada, there is likely considerable variation in the frequency of blood cultures performed for nonhospitalized febrile children, but more research is still needed to quantify this variation and account for how it can affect the estimated incidence. In one study, prevalence of occult pneumococcal bacteremia in febrile children presenting to pediatric emergency departments was at least 2%, but the risk of adverse outcome was very low (28). This reflects the hypothesis that missed cases of bacteremia due to nonperformance of blood culture contribute less to the global burden of disease than confirmed cases.

For pneumonia from all causes, rates in Canada are very similar to those reported in a prospective population-based study in Finland (19). In our study, medical administrative data systems were used to obtain the number of nonhospitalized cases. This source did not describe the methods and criteria used by physicians to diagnose pneumonia. The proportion of non-bacteremic pneumonia attributable to *S pneumoniae* is an uncertain parameter in our analysis, as a large range of values has been reported (9-16). For AOM from all causes, rates are very close to those observed in a prospective study of children in Boston (29), and the attributable fraction was chosen on the basis of a very good prospective etiological study of AOM in Finland (6). MVTs are a parameter for which there seems to be a variation from province to province, especially in the proportion of MVTs performed in a nonhospital setting. A study conducted in Calgary by Desai et al (30) reported that as many as 19% of MVTs were performed in nonhospital settings, including 9% of MVTs in infants under one year of age.

This study tried to evaluate all the important parameters of the burden of pneumococcal diseases in Canadian children. Many Canadian sources of information were used and ad hoc studies were conducted when no data were available. There are, however, some limits in the methodologies used. For example, the limited size of our sample in the cost evaluation of nonhospitalized cases of otitis and pneumonia, and the retrospective aspect of the telephone survey could lead to some imprecision in the results.

Besides PCV-7, varicella and conjugate serogroup C meningococcal vaccines have been proposed for use in publicly funded immunization programs for children in Canada (31,32). Pneumococcal infections do not cause epidemics, and the number of deaths and disabilities is low — a consequence of the effectiveness of treatments. For these reasons, there is not a strong demand for the use of pediatric pneumococcal vaccines in the population. In a 2002 Quebec survey, 86% of respondents supported the inclusion of meningococcal vaccine in routine childhood immunization, but only 60% supported a vaccine against pneumonia (a proxy of pneumococcal infection) and 41% supported a vaccine against chickenpox (33).

CONCLUSION

The epidemiological burden of pneumococcal infections in Canadian children is important and associated costs are significant, both for the families and the health system. It is worthwhile to prevent these conditions using PCV-7 in publicly-funded immunization programs throughout Canada. The effectiveness of this vaccine has been demonstrated in randomized trials (4-6). The next step of our research program will be a cost-effectiveness analysis, using a simulation model and input variables taken from the present study.

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