ORIGINAL ARTICLE

The burden of pneumococcal disease in the Canadian population before routine use of the seven-valent pneumococcal conjugate vaccine

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BACKGROUND: In the United States, implementation of the seven-valent conjugate vaccine into childhood immunization schedules has had an effect on the burden of pneumococcal disease in all ages of the population. To evaluate the impact in Canada, it is essential to have an estimate of the burden of pneumococcal disease before routine use of the vaccine.
METHODS: The incidence and costs of pneumococcal disease in the Canadian population in 2001 were estimated from various sources, including published studies, provincial databases and expert opinion.
RESULTS: In 2001, there were 565,000 cases of pneumococcal disease in the Canadian population, with invasive infections representing 0.7%, pneumonia 7.5% and acute otitis media 91.8% of cases. There were a total of 3000 deaths, mainly as a result of pneumonia and largely attributable to the population aged 65 years or older. There were 54,330 life-years lost due to pneumococcal disease, and 37,430 quality-adjusted life-years lost due to acute disease, long-term sequelae and deaths. Societal costs were estimated to be $193 million (range $155 to $295 million), with 82% borne by the health system and 18% borne by families. Invasive pneumococcal infections represented 17% of the costs and noninvasive infections represented 83%, with approximately one-half of this proportion attributable to acute otitis media and myringotomy.
CONCLUSIONS: The burden of pneumococcal disease before routine use of the pneumococcal conjugate vaccine was substantial in all age groups of the Canadian population. This estimate provides a baseline for further analysis of the direct and indirect impacts of the vaccine.

Key Words: Burden; Canada; Pneumococcal disease; Vaccine

Le fardeau de la maladie à pneumocoque au sein de la population canadienne avant l'utilisation systématique du vaccin conjugué heptavalent contre le pneumocoque

HISTORIQUE : Aux États-Unis, l'implantation du vaccin conjugué heptavalent dans les calendriers de vaccination pour enfants a eu un effet sur le fardeau de la maladie à pneumocoque au sein de la population de tout âge. Pour en évaluer les répercussions au Canada, il est essentiel d'estimer le fardeau de la maladie à pneumocoque avant l'utilisation systématique du vaccin.
MÉTHODOLOGIE : On a estimé l'incidence et le coût de la maladie à pneumocoque au sein de la population canadienne en 2001 auprès de diverses sources, y compris les études publiées, les bases de données provinciales et l'opinion d'experts.
RÉSULTATS : En 2001, on a recensé 565 000 cas de maladie à pneumocoque au sein de la population canadienne, les infections envahissantes représentant 0,7 % des cas, les pneumonies, 7,5 % et l'otite moyenne aiguë, 91,8 %. Au total, 3 000 personnes sont décédées, principalement en conséquence d'une pneumonie et dans la population de 65 ans et plus. On a répertorié 54 330 années de vie perdues en raison de la maladie à pneumocoque, et 37 430 années de vie pondérées par la qualité perdues en raison d'une maladie aiguë, de séquelles à long terme et des décès. On a évalué les coûts sociétaux à 193 millions de dollars (plage de 155 millions de dollars à 295 millions de dollars), 82 % étant assumés par le système de santé et 18 %, par les familles. Les infections à pneumocoque envahissantes représentaient 17 % des coûts, et les infections non envahissantes, 83 % des coûts, environ la moitié de cette proportion étant attribuable à l'otite moyenne aiguë et à la paracentèse.
CONCLUSIONS : Le fardeau de la maladie à pneumocoque avant l'utilisation systématique du vaccin conjugué contre le pneumocoque était considérable dans tous les groupes d'âge de la population canadienne. La présente évaluation fournit des données de base pour procéder à une analyse plus approfondie des répercussions directes et indirectes du vaccin.

Aseven-valent pneumococcal conjugate vaccine (PCV-7) was licensed in Canada in 2001 (1). Alberta was the first province to introduce PCV-7 into its publicly funded routine immunization schedule in September 2002 (2), and it has been included in the vaccination schedules of all provinces since December 2005 (3). In the United States, the introduction of the vaccine into routine childhood immunization schedules in 2000 was followed by a marked decrease in the incidence of invasive pneumococcal disease in all ages of the population (4,5). To evaluate the real direct and indirect impacts of PCV-7 in Canada, it is necessary to estimate the burden of pneumococcal disease for all ages before vaccine implementation.

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However, there exist few fragmented data on the burden of pneumococcal disease in the Canadian population. A study was conducted on children nine years of age or younger in 2000 (6), and on children 12 years of age or younger from 1994 to 1998 (7). The objective of the present study was to estimate the epidemiological and economic burden of pneumococcal disease for all ages of the Canadian population before the implementation of PCV-7 into vaccine programs.

METHODS

Epidemiological parameters

The analysis was based on the 2001 Canadian population estimates (8), before significant use of the vaccine. The major pneumococcal-associated illnesses were included in the analysis based on the availability of epidemiological vaccine effectiveness data (9,10). Mutually exclusive outcomes, categorized hierarchically, included pneumococcal meningitis and pneumococcal bacteremia with or without pneumonia, pneumonia without bacteremia, acute otitis media (AOM) and myringotomy with ventilation tube insertion (MVT). Sinusitis was the only common pneumococcal manifestation not included in the analysis, because the incidence and proportion of infections caused by *Streptococcus pneumoniae* are unknown. Other manifestations (eg, bone and joint, and cardiovascular infections) are generally rare and thus were not included.

Invasive disease

For children younger than 16 years of age, the age-specific incidence of pneumococcal disease has been calculated by Petit et al (6). For those aged 16 years or older, the incidence of invasive pneumococcal disease was estimated from various sources. Population-based, age-specific invasive pneumococcal disease rates were available for the Calgary, Alberta, area for the years 1998 to 2001 (Jim Kellner, personal communication). The proportion of invasive pneumococcal disease diagnosed as meningitis and bacteremia was calculated using American data from the Active Bacterial Core Surveillance/Emerging Infections Program Network (11). This proportion was applied to the Calgary area data. The percentage of cases hospitalized for bacteremia among children 16 years of age or younger was estimated to be 62% by combining data from three different data sources: the Quebec Provincial Notifiable Diseases Database, the Quebec Provincial Reference Laboratory and the Immunization Monitoring Program ACTive (IMPACT) (6). For adults 18 years of age or older, the percentage hospitalized was determined to be 83.7% from a prospective study conducted in the Edmonton, Alberta, area (12).

Pneumonia

The incidence of all-cause hospitalized pneumonia cases was determined from the Quebec hospital administrative data system (Med-Echo) from the years 1991 to 2001 using ICD-9 codes 480.0 to 486.9 for the primary diagnosis. To determine the incidence of all-cause nonhospitalized pneumonia cases, the ratio of hospitalized to nonhospitalized pneumonia cases was determined from a population-based study conducted in Finland (13) and then applied to the Canadian data. The proportion of hospitalized pneumonia due to *S pneumoniae* in children 16 years of age or younger has been estimated to be 22% by Petit et al (6). However, the proportion of pneumonia attributable to *S pneumoniae* is an uncertain parameter. Therefore, a sensitivity analysis was conducted by varying these values between a lower value of 13% (14) and an upper value of 37% (15). For individuals 17 years of age or older, the fraction of hospitalized pneumonia due to *S pneumoniae* was

determined to be 17% based on a meta-analysis of 10 selected studies that defined the etiology of community-acquired pneumonia requiring hospitalization, and the CI of this estimate was used to define the lower (13%) and upper (35%) values (16).

AOM and MVT

The age-specific incidence for AOM and MVT from two months to nine years of age has been previously determined using data from Manitoba and Quebec (6). The percentage of AOM cases due to *S pneumoniae* has been determined in a prospective study in Finland, in which pneumococcal etiology was identified in 30.8% of AOM cases (17). Because this is another uncertain parameter, a sensitivity analysis was conducted using a lower limit of 28% (18) and an upper limit of 35% (19,20). The age-specific, global MVT incidence was determined using data from the Med-Echo system, as well as from expert consultation (6). The proportion of MVT procedures resulting from *S pneumoniae* was estimated to be 50% by expert opinion (21). A range of 50% was assumed due to the uncertainty of this parameter; thus, upper and lower limits of 75% and 25% were used, respectively. AOM and MVT outcomes were not included for individuals older than nine years of age, because the disease is less common in school-aged children and adolescents, and is infrequent in adults (22).

Mortality

A case fatality rate for pneumococcal meningitis among children 17 years of age or younger was determined to be 6.5% from a survey conducted among 11 pediatric centres of IMPACT (jointly sponsored by the Canadian Paediatric Society and the Laboratory Centre for Disease Control), including academic centres located across Canada, and accounts for approximately 85% of the tertiary care pediatric beds in Canada (23). For adults 18 years of age or older, a case fatality rate of 27.6% was estimated by determining a weighted average from several studies (24-26). The case fatality rate for hospitalized pneumococcal bacteremia for children nine years of age or younger was estimated to be 2% from Canadian population-based surveillance data (23), and the case fatality rate for hospitalized pneumococcal pneumonia for the same age group was determined to be 1% from a population-based study conducted in Finland (13). For individuals 10 to 18 years of age, 18 to 64 years of age, and 65 years of age or older, the case fatality rates for pneumonia and bacteremia were 1.6%, 15% and 31%, respectively, as determined by *S pneumoniae* surveillance in the province of Quebec (27). It was assumed that there were no deaths due to nonhospitalized outcomes. The life expectancy of Canadians at different ages were used to calculate the life-year loss from pneumococcal disease-associated deaths (28).

Morbidity

A deafness rate of 13% resulting from meningitis for children 17 years of age or younger was determined from a meta-analysis of randomized clinical trials (29). For adults 18 years of age or older, a deafness rate of 26% was determined (24,25). A neurological disability rate of 7% (30) was used for survivors of meningitis 17 years of age or younger, and 19% was used for adults 18 years of age or older (24,25). The utility values for survivors of meningitis were also determined. Hearing loss was considered to be a mild disability state, valued at 0.8, while neurological sequelae were considered to be severe, valued at 0.6 (a value of 0 corresponds to death and 1 to perfect health) (31). For acute disease, the coefficients used for quality-adjusted life-year loss were 0.0079 for

hospitalized bacteremia, 0.0232 for meningitis, 0.004 for nonhospitalized pneumonia, 0.006 for hospitalized pneumonia and 0.005 for otitis media (32). The quality-adjusted life-year loss was then calculated based on the disability-free life expectancy of Canadians (33).

Economic parameters

Financial costs are expressed in Canadian dollars for the year 2001, and any prices used from before or after this year were adjusted using the Canadian price index for health and personal care (34).

Costs for hospitalization 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 bacteremia (ICD-9 code 038.2) and pneumococcal pneumonia (ICD-9 code 481.9) as a primary diagnosis were identified, and mean values of hospitalization costs were calculated. Physician fees were determined from the *National Grouping System Categories Report, Canada, 2001–2002* (35). It was assumed that for each diagnostic category, the patient would have had both a consultation and a major assessment on the first day of hospitalization, and would have been seen once daily for the remainder of the hospital stay by either an internist or a pediatrician. For patients diagnosed with meningitis, a major assessment by a neurologist was also included. For all hospitalized cases, the cost of one outpatient visit to either a family practitioner or pediatrician was also included, as well as the cost of a follow-up visit to a neurologist for cases of meningitis. The median length of hospital stay for individuals 19 years of age or younger was determined to be 11.5 days for meningitis, and three days for bacteremia and pneumonia (36). For adults 20 years of age or older with pneumonia and bacteremia, the median length of stay was determined to be five days (37), and for meningitis, 11.5 days (38). The long-term specialized schooling and medical costs for disability and deafness caused by meningitis were also included. The cost of special education for a duration of 12 years for children with bilateral deafness ($10,000/year) was estimated from data provided by the Ministry of Education in Quebec (39). It was estimated that one-half of deafness cases resulting from pneumococcal meningitis were bilateral (40). The cost of specialized schooling associated with neurological disability was estimated using data from a study on birth defects in the United States (US$200,000/case) (41). These costs were included in the average unit health care cost of pneumococcal meningitis (39). For adults 20 years of age or older, only the associated long-term medical costs were included, and for those 65 years of age or older, the value was halved to account for survival.

The direct and indirect costs assumed by families for children hospitalized with pneumococcal disease have been estimated by Petit et al (6). In the present study, only the direct costs were included due to a lack of data concerning the indirect costs associated with pneumococcal disease in adults. Family costs for hospitalized bacteremia and pneumonia in individuals 65 years of age or older were estimated from a study conducted in Edmonton on the private costs incurred by patients hospitalized with community-acquired pneumonia (42).

The costs incurred by the health care system for children with nonhospitalized pneumococcal disease were estimated from the doctor and family phone survey conducted by Petit et al (6). For adults, the cost was estimated by determining the price of medications used to treat these diseases. The costs associated with MVT have been previously estimated by Petit et al (6).
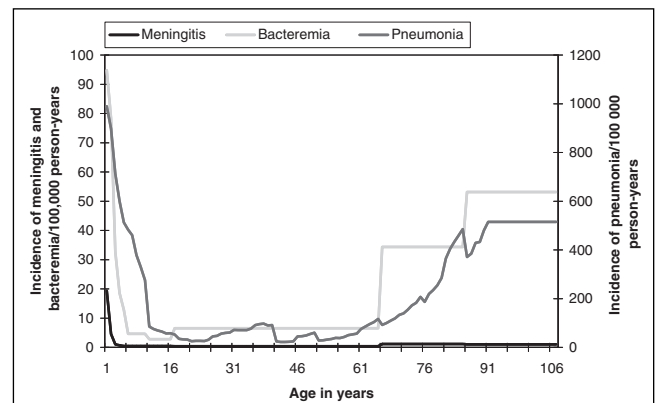

Figure 1) *Age-specific incidence of pneumococcal meningitis, bacteremia and pneumonia in the Canadian population in 2001*

RESULTS

The incidence of pneumococcal meningitis, bacteremia and pneumonia are presented in Figure 1. Disease incidence is high at a young age and then decreases significantly. Later in life (at approximately 65 years of age), the incidence begins to increase again, most dramatically for bacteremia and pneumonia. The estimated number of cases of pneumococcal-related outcomes in the Canadian population for the year 2001 are presented by age group in Table 1. The large number of cases affecting children under one year of age demonstrates the high incidence at this young age. For all age groups, meningitis represents the smallest proportion of cases of pneumococcal disease, while AOM, although assumed to occur only until nine years of age, represents the largest proportion by far, with a total of 518,801 cases (86%) (Table 1).

Over a period of one year, a total of 38 deaths were attributed to meningitis, 545 deaths to bacteremia and 2419 to pneumonia. Deaths resulting from bacteremia and pneumonia were largely attributable to the population aged 65 years or older (data not presented in the tables). In addition, there were a total of 54,330 life-years lost due to pneumococcal disease (range 44,895 to 96,193), and 37,430 quality-adjusted life-years lost due to acute disease, long-term sequelae and deaths (range 31,102 to 62,510). The burden of disease expressed in quality-adjusted life-years is less than the burden expressed in life-years lost due to the decrease in average quality of life associated with aging.

The unitary costs to the health care system for pneumococcal disease are presented in Table 2, and the unitary costs to families are presented in Table 3. The unitary cost of meningitis for the health care system is significant, because the costs of resulting sequelae are also included. The costs to families are highest for hospitalized outcomes, with meningitis being the most costly.

The total burden of pneumococcal disease in the Canadian population for 2001 by age category is presented in Table 4. Although AOM has a relatively low family and health care system unit cost, due to the high number of cases, it represented a significant proportion of the burden until nine years of age. Among adults, hospitalized pneumococcal pneumonia carried the highest societal burden (Table 4). The overall societal costs of all cases of pneumococcal disease (including MVT) amounted to $193 million, with 82% borne by the health care system and 18% borne by families (Table 4). Invasive pneumococcal infections had an overall disease cost of over $32 million, which was 17% of the total costs. A very large proportion of this

TABLE 1
Estimated number of cases of pneumococcal disease in the Canadian population in 2001

	Younger than one year of age (n)	One to four years of age (n)	Five to nine years of age (n)	10 to 19 years of age (n)	20 to 64 years of age (n)	65 years of age or older (n)	Total (n)
Canadian population	332,343	1,426,853	2,016,678	4,195,568	19,126,747	3,923,116	31,021,305
Hospitalized meningitis	64	24	9	17	67	45	226
Hospitalized bacteremia	195	309	58	131	1052	1195	2940
Nonhospitalized bacteremia	120	190	36	51	205	233	833
Hospitalized pneumonia	819	1762	768	330	2679	6469	12,827
Lower limit	484	1041	454	205	2049	4947	9180
Upper limit	1377	2963	1292	577	5516	13,319	25,044
Nonhospitalized pneumonia	2471	7896	6966	2026	7580	2509	29,449
Lower limit	1460	4666	4116	1261	5796	1919	19,218
Upper limit	4156	13,280	11,715	3545	15,605	5166	53,468
Acute otitis media	120,643	253,353	144,805				518,801
Lower limit	109,676	230,321	131,641				471,638
Upper limit	137,095	287,901	164,551				589,547
Total	124,313	263,534	152,642	2555	11,583	10,451	565,077
Lower limit	112,000	236,551	136,314	1665	9169	8338	504,036
Upper limit	143,008	304,667	177,661	4322	22,445	19,957	672,060
Myringotomy*	804	17,691	16,400				34,895
Lower limit	402	8846	8200				17,447
Upper limit	1205	26,537	24,599				52,342

Myringotomy is not included in total because it is a procedure associated with acute otitis media

TABLE 2
Unitary costs to the health care system for pneumococcal disease

	Younger than one year of age	One to four years of age	Five to nine years of age	10 to 19 years of age	20 to 64 years of age	65 years of age or older
Meningitis	$30,284	$30,996	$28,859	$28,859	$12,399	$9,891
Hospitalized bacteremia	$7,337	$4,131	$4,488	$4,488	$10,233	$9,876
Nonhospitalized bacteremia	$125	$125	$125	$125	$125	$125
Hospitalized pneumonia	$1,994	$2,707	$3,775	$6,269	$6,671	$7,027
Nonhospitalized pneumonia	$87	$87	$87	$87	$87	$87
Acute otitis media	$60	$60	$60			
Myringotomy	$539	$539	$539			

cost was borne by the health care system (96%). Noninvasive infections amounted to more than $160 million (83% of total costs), with approximately 50% the costs due to AOM and MVT combined, and the other 50% due to pneumonia. Of these costs, 79% was borne by the health care system.

DISCUSSION

The aim of the present study was to complete the data on the epidemiological and economic burden of pneumococcal disease in the Canadian population that have been determined for children nine years of age or younger (6), because few data exist for the adult population. In the study, all age groups were considered, so that the indirect effect of childhood vaccination with PCV-7 on the adult population could then be assessed. The outcomes evaluated in the study were restricted to those used in the childhood analysis (pneumococcal meningitis, bacteremia, pneumonia and otitis) (6). However, in contrast to the childhood analysis, the long-term costs associated with health care and specialized schooling for neurological disability and hearing loss resulting from meningitis

were included, while indirect costs, such as productivity losses due to pneumococcal disease, were not. As in the previous study, there were no cost values assigned for the resulting pain, sorrow, anxiety and interpersonal tensions caused by pneumococcal disease (6).

The incidence rates of pneumococcal infections estimated in the present study are comparable with those observed in a cohort model study that evaluated the prevaccination pneumococcal epidemiology in England and Wales (43). Meningitis, bacteremia, pneumonia and otitis media were also used as outcomes in that study. However, the percentage of pneumonia and otitis cases attributed to *S pneumoniae*, a factor that heavily influences the determination of disease incidence, differed slightly between the two studies. The English study estimated the proportion of pneumonia cases caused by *S pneumoniae* to be 26% for all age groups, while the present study used more conservative values (22% for individuals 17 years of age or younger [6] and 17% for those 18 years of age or older in the baseline analysis [16]). In contrast, the proportion of AOM due to *S pneumoniae* was estimated to be 23% by the English study,

TABLE 3
Unitary costs to families for pneumococcal disease

	Younger than one year of age	One to four years of age	Five to nine years of age	10 to 19 years of age	20 to 64 years of age	65 years of age or older
Meningitis	$797	$797	$797	$797	$797	$797
Hospitalized bacteremia	$266	$266	$266	$266	$266	$603
Nonhospitalized bacteremia	$77	$77	$77	$77	$119	$119
Hospitalized pneumonia	$266	$266	$266	$266	$266	$603
Nonhospitalized pneumonia	$77	$77	$77	$77	$119	$119
Acute otitis media	$45	$45	$45			
Myringotomy	$45	$45	$45			

TABLE 4
Total burden of pneumococcal disease in the 2001 Canadian population by age group and fraction borne by the health system

	Younger than one year of age	One to four years of age	Five to nine years of age	10 to 19 years of age	20 to 64 years of age	65 years of age or older	Total	Borne by health system
Hospitalized meningitis	$2,001,000	$752,000	$275,000	$517,000	$883,000	$477,000	$4,905,000	96%
Hospitalized bacteremia	$1,485,000	$1,361,000	$276,000	$622,000	$11,042,000	$12,521,000	$27,307,000	96%
Nonhospitalized bacteremia	$24,000	$38,000	$7,000	$10,000	$50,000	$57,000	$186,000	56%
Hospitalized pneumonia	$1,850,000	$5,236,000	$3,104,000	$2,155,000	$18,584,000	$49,355,000	$80,284,000	93%
Lower limit	$1,093,000	$3,094,000	$1,834,000	$1,341,000	$14,212,000	$37,742,000	$59,316,000	93%
Upper limit	$3,112,000	$8,805,000	$5,220,000	$3,771,000	$38,262,000	$101,613,000	$160,783,000	93%
Nonhospitalized pneumonia	$405,000	$1,293,000	$1,141,000	$332,000	$1,562,000	$517,000	$5,250,000	49%
Lower limit	$239,000	$765,000	$674,000	$207,000	$1,194,000	$395,000	$3,474,000	48%
Upper limit	$681,000	$2,175,000	$1,919,000	$581,000	$3,215,000	$1,064,000	$9,635,000	48%
Acute otitis media	$12,709,000	$26,690,000	$15,255,000				$54,654,000	57%
Lower limit	$11,554,000	$24,264,000	$13,868,000				$49,686,000	44%
Upper limit	$14,443,000	$30,330,000	$17,335,000				$62,108,000	57%
Myringotomy	$469,000	$10,329,000	$9,575,000				$20,373,000	92%
Lower limit	$235,000	$5,165,000	$4,787,000				$10,187,000	92%
Upper limit	$704,000	$15,494,000	$14,362,000				$30,560,000	92%
Total	$18,943,000	$45,699,000	$29,633,000	$3,636,000	$32,121,000	$62,927,000	$192,959,000	82%
Lower limit	$16,631,000	$35,438,000	$21,722,000	$2,697,000	$27,381,000	$51,193,000	$155,062,000	77%
Upper limit	$22,449,000	$58,955,000	$39,395,000	$5,501,000	$53,452,000	$115,733,000	$295,485,000	84%

Costs rounded off to the closest thousandth dollar

while a more significant proportion (31% [17]) was attributed to AOM in the present study.

Surveillance by the American Active Bacterial Core Surveillance/Emerging Infections Program Network also determined the prevaccination incidence of invasive pneumococcal infections (11). There was substantial racial disparity in the disease incidence between the African-American and non-African-American populations in all age groups (the incidence of invasive disease was approximately 2.5 times greater in the African-American population). However, when the incidence of the non-African-American population was compared with the incidence of the Canadian population determined in this study, the incidence rates were more comparable (the Canadian incidence rates were only slightly lower). The difference may be due to intercountry variations in diagnostic and surveillance practices. In addition, comparable disease incidence rates between countries are not necessarily an indicator that variations do not exist; thus, interstudy comparisons must be regarded cautiously.

The present study attempted to include all relevant and important parameters of the burden of pneumococcal disease in the Canadian population before the routine use of PCV-7. Many of the data are of Canadian origin, thus providing a better estimate of the burden of pneumococcal disease in this population. Although Canadian data were favoured over other sources, some American and Finnish data were used when this was not practical or possible. The limitations of the American data are described above. Furthermore, although not ideal, the Finnish data are most likely very applicable to the Canadian population, because the pneumococcal epidemiology and socioeconomic situation of the two countries are similar. A better integration of Canadian laboratory and administrative databases would assist in determining data specific to this country. There are certain limitations in the methodology of the analysis. Some of the values used were estimates made by experts when necessary data were not available, and the indirect costs, such as productivity losses resulting from disease, were also not included. However, the study covered all ages in the population, and the incidence of disease was mainly

concentrated at the extremes of the age spectrum (infancy and advanced age). Therefore, individuals who are generally not employed and thus have minimal productivity losses represent the largest proportion of cases. In addition, some economic analysts have argued that productivity losses should not be included, because this may lead to double counting if quality-adjusted life-years lost are expressed (44). The exclusion of deaths from nonhospitalized outcomes due to a lack of data is another study limitation. *S pneumoniae* is certainly a significant source of fatal pneumonia cases among elderly people dying at home or in long-term care facilities; thus, mortality has most likely been underestimated in this age group.

CONCLUSIONS

The burden of pneumococcal infections in the Canadian population before routine use of PCV-7 was substantial for both families and the health care system. Determining this prevaccinal measurement of pneumococcal disease burden thus provides a baseline for future analyses concerning the effects of childhood PCV-7 use on the entire Canadian population.

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