A Cost-effectiveness Analysis of Pneumococcal Vaccination in Street-involved, HIV-infected Patients

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A B S T R A C T

Background: Delivery of the pneumococcal vaccine (PCV) to street-involved, HIV patients in British Columbia is low due to poor compliance. Since the use of PCV is expected to reduce morbidity and mortality, it may be more cost-effective to provide the vaccine directly to clinics.

Methods: Three strategies were compared for a cohort of 5000 patients: 1) administering PCV at the clinics; 2) giving a prescription for PCV and expecting patients to fill it at a pharmacy and return for administration; and 3) no administration of vaccine. Decision analysis was utilized to map the costs and outcomes of the patients over 5 years and conduct an incremental cost-effectiveness analysis from the perspective of the Ministry of Health.

Results: The average cost per patient was the lowest in Strategy 1 ($549) compared to Strategy 2 ($702) and Strategy 3 ($714). For the cohort, Strategy 1 prevented 269 and 299 additional cases of pneumococcal disease and resulted in a cost savings of $535,000 and $595,000 in direct medical costs when compared to Strategies 2 and 3, respectively. The model was robust to extensive sensitivity analyses.

Conclusions: The Ministry of Health should supply PCV to clinics involved in the care of street-involved HIV patients as this is the most cost-effective strategy.

A B R É G É

Contexte : L'administration du vaccin antipneumococcique (PCV) aux patients de la rue atteints du VIH, en Colombie-Britannique est faible en raison du manque d'assiduité. Il serait plus rentable de fournir le vaccin directement aux cliniques, étant donné que le vaccin PCV est censé réduire la morbidité et la mortalité.

Méthodes : Nous avons mis trois stratégies à l'épreuve, auprès d'une cohorte de 5 000 patients : 1) administrer le PCV en clinique, 2) remettre une ordonnance pour le vaccin PCV au patient et s'attendre à ce qu'il la fasse compléter à la pharmacie et revienne pour le recevoir, et 3) ne pas administrer le vaccin. L'analyse de décision a servi à établir les coûts et les résultats chez les patients pendant plus de cinq ans et d'effectuer une analyse de rentabilité du point de vue du Ministre de la santé.

Résultats : Le coût moyen par patient était le plus bas dans la première stratégie (549 $) comparativement à 702 $ dans la deuxième et à 714 $ dans la troisième stratégie. Pour ce qui est de la cohorte, la première stratégie a prévenu l'apparition de 269 cas puis de 299 autres cas d'infection pneumococcique, entraînant des économies de 535 000 $ et de 595 000 $ respectivement en coûts médicaux directs si on les compare aux stratégies 2 et 3. Le modèle utilisé était robuste jusqu'à la généralisation de l'analyse de sensibilité.

Conclusions : La stratégie la plus rentable pour le Ministre de la santé devrait consister à alimenter en vaccin PCV les cliniques qui sont impliquées dans les interventions de rue auprès des patients atteints du VIH.

Infections due to *Streptococcus pneumoniae* remain a major cause of morbidity, mortality and health care expenditure around the world. *S. pneumoniae* is an important cause of meningitis, otitis media, sinusitis, pneumonia and bacteremia in adults and children. In the developed countries, invasive disease due to *S. pneumoniae* is a serious problem among the elderly, infants, individuals with chronic underlying conditions or those who are immunosuppressed, including patients infected with the human immunodeficiency virus (HIV).

Pneumonia is the most commonly diagnosed bacterial respiratory infection in HIV-infected persons.[1] As in the general population, *S. pneumoniae* is the most common bacterial pathogen identified in these patients with community-acquired pneumonia. Population-based studies suggest that bacterial pneumonia occurs much more commonly among HIV-infected individuals than in the non-HIV-infected population.[2-8] The predisposition to invasive pneumococcal disease during HIV infection is due to dysfunctional host defenses rather than increased bacterial exposure or colonization.[9]

The increased rate of pneumococcal pneumonia in the HIV-infected population makes prevention an important aspect of care for this patient group. For this reason, the Advisory Committee on Immunization Practices (ACIP) recommends the use of the 23-valent pneumococcal polysaccharide vaccine for all symptomatic or asymptomatic HIV-infected patients at the time of their diagnosis.[10] However, this recommendation is based on a potential but unproven benefit of the vaccine in this population (since efficacy studies of the pneumococcal vaccine are lacking in patients with HIV infection) and on the lack of serious adverse effects with the pneumococcal vaccine.[11]

At the present time, delivery of the pneumococcal vaccine to street-involved, HIV-infected persons attending downtown clinics in British Columbia is poor (approximately 10%).[12] Patients are required to obtain prescriptions from the clinics, fill their prescriptions for the vaccine at a nearby pharmacy and return to downtown clinics for administration. Even though many will receive social assistance in paying for the vaccine, the procedure is cumbersome and the necessity for personally procuring vaccine is a barrier to compliance for those with chaotic lives. Despite the availability of newer highly active antiretroviral therapy (HAART), these patients are typically noncompliant and do not receive these agents.[13]

The use of the pneumococcal vaccine might reduce morbidity, mortality, and associated health-related costs. Provision of

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the vaccine directly to the downtown clinics could prove more cost-effective than the prescription method as it may remove barriers to immunizing a larger proportion of patients.

OBJECTIVE

The objective of this study was to examine the incremental cost-effectiveness of three different strategies of a pneumococcal immunization program from the perspective of the British Columbia Ministry of Health in street-involved, HIV-positive patients attending the downtown clinics in Vancouver, British Columbia.

METHODS

Patients

A hypothetical cohort of 5,000 representing the estimated number of HIV-infected, street-involved patients attending the downtown clinics was treated according to the model.

Decision analysis model

The economic analysis was conducted from the perspective of the Ministry of Health. A decision model was utilized to map the cost-effectiveness of three different strategies over time (Figure 1): 1) stocking all downtown clinics with the pneumococcal vaccine and administering it to all HIV-infected patients; 2) giving a prescription to HIV patients for the pneumococcal vaccine, expecting them to fill this at a pharmacy and come back to the clinic for administration by the physician; and 3) not administering the pneumococcal vaccine to any HIV-infected patient. During each year, the patients in each cohort could transition between pneumococcal disease or healthy state. Each of the cohorts were further subdivided according to CD4 lymphocyte count since some of these patients may be on PCP prophylaxis with trimethoprim-sulfamethoxazole which has been shown to be protective against *S. pneumoniae* infections.[4]

Probability estimates

Probability estimates for the model (Table I) were derived from published reports identified in the MEDLINE database (1966 to 1999 - using keywords "pneumococcus", "pneumonia", "*Streptococcus pneumoniae*", "cost-effectiveness", "decision analysis", "pneumococcal vaccine", "human immunodeficiency virus"), B.C. Centre for Disease Control, Centre for Excellence in HIV/AIDS and Vancouver Hospital and Health Sciences Centre. In areas where a probability could be determined from these sources, estimates were derived from the best available sources and included the use of unpublished data or a modified Delphi process interview of experts.[14]

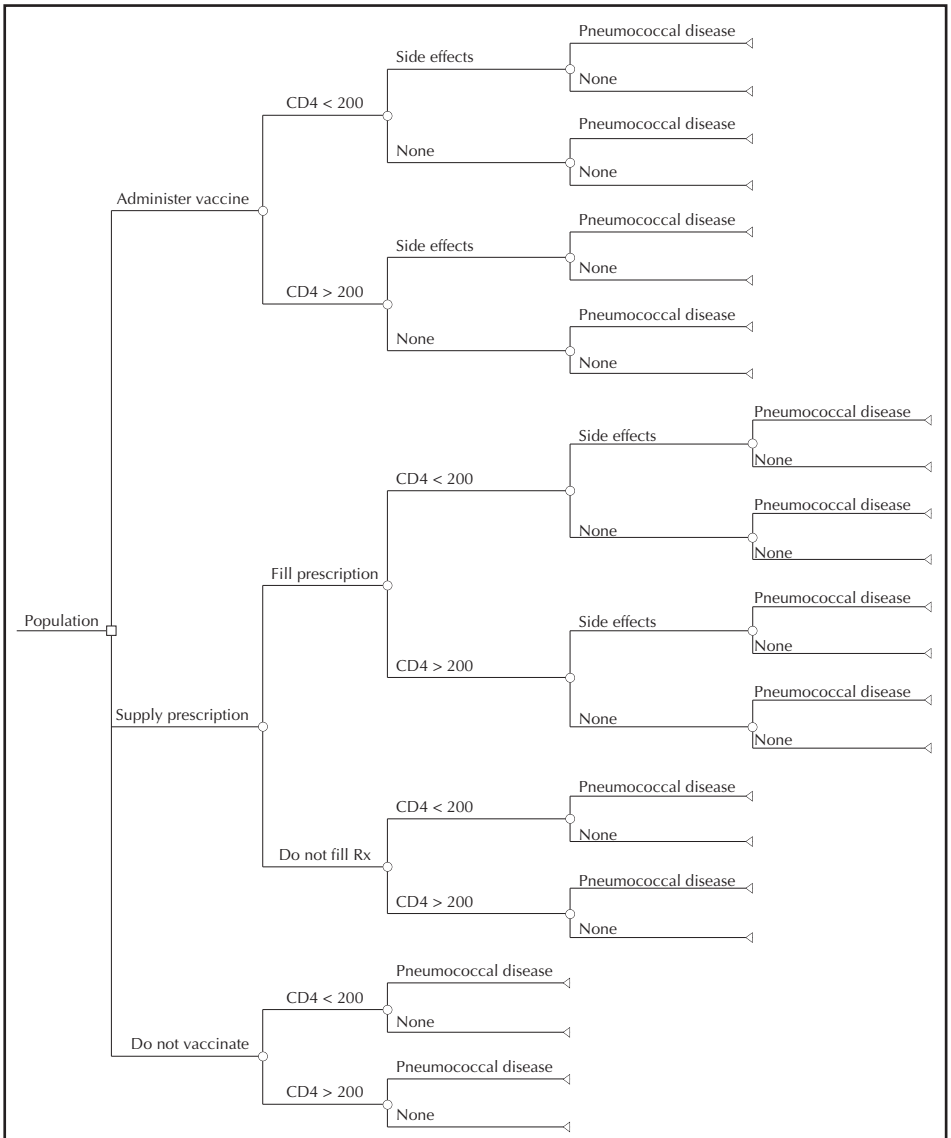

Figure 1. Decision tree

Probabilities of pneumococcal pneumonia and PCP prophylaxis

S. pneumoniae is the leading cause of community-acquired pneumonia and bacteremia in HIV patients; rates of pneumococcal pneumonia and bacteremia are more than 10-100 times greater in these patients than in HIV-seronegative controls with the reported rates ranging from 802.9 to 4,550 per 100,000 patient years.[2-8] In addition, the rate of bacterial pneumonia in HIV patients is increased with lower CD4 lymphocyte counts: patients with CD4 < 200/mm^3 have a greater risk of developing bacterial pneumonia, however, prophylaxis with trimethoprim-sulfamethoxazole is associated with a 67% reduction in episodes of bacterial pneumonia.[4] For this analysis, the annual incidence and mortality rates for pneumococcal pneumonia and bacteremia in HIV

TABLE I
Assumptions for the Base-case Analysis and Sensitivity Analysis

Variables	Base Case Probability Estimate	Sensitivity Analysis Low	Sensitivity Analysis High	Reference
Pneumococcal bacteremia (Incidence per 100,000)	940	840	1040	Witt DJ, Polsky B, Hirschtick RE, Garcia-Leoni ME, Schuchat A, Redd SC,
Pneumococcal pneumonia (Incidence per 100,000)	4550	800	5550	Nuorti JP
Bacterial pneumonia (Incidence per 100,000)				Hirschtick RE
CD4 count > 500/mm^3	2300	1300	3300	
CD4 count 200-500/mm^3	6800	5800	7800	
CD4 count < 200/mm^3	10800	9800	11800	
Case fatality (%)				Hirschtick RE,
Bacterial pneumonia	5	5	30	Janoff EN
Incidence of bacterial pneumonia in patients on trimethoprim-sulfamethoxazole for PCP prophylaxis (%)	33	14	73	Hirschtick RE
Patients with CD4 count (%)				BCCDC, BCCE
< 200/mm^3	23	15	50	
> 200/mm^3	77	50	85	
Compliance (%)				Assumption
PCP prophylaxis	100	25	100	
Treatment of pneumococcal pneumonia (%)				BCCDC, BCCE
Inpatient	20	5	20	
Outpatient	80	50	95	
Vaccine Effect (%)				Shapiro ED, Butler JC
Effectiveness	20	0	67	
Vaccine Protection (years)				Hilleman MR, Kraus C
Duration of protection	5	0	10	
Vaccine (%)				CDC, Fine MJ
Side effects	33	20	100	
Compliance (%)				BCCDC, BCCE
Filling prescription of pneumococcal vaccine	10	0	100	
Treatment of pneumococcal disease ($)				BCCDC, VGH,
Inpatient care	9634.24	6254	11269	Expert Opinion
Outpatient care	243.54	156	289	
Cost of PCP prophylaxis ($)				BCCDC
Trimethoprim-sulfamethoxazole	40.15	26.15	56.15	
Treatment of vaccine side effects ($)	1.15	0	2.36	BCCDC, BCCE
Vaccine cost ($)				BCCDC
23-valent pneumococcal vaccine	8.25	5.36	11.19	

patients were obtained from surveillance studies conducted between 1983 and 1987 and, to be conservative, we assumed all patients with CD4 lymphocyte counts less than 200/mm^3 were on PCP prophylaxis with 100% compliance. This assumption was thoroughly tested with sensitivity analysis. We assumed that patients who were expected to get their pneumococcal vaccine prescription filled had a 10% compliance rate based on data available from B.C. Centre for Disease Control and B.C. Centre for Excellence.

Vaccine efficacy and duration of effect

The currently available pneumococcal vaccine includes 23 purified capsular polysaccharide antigens of *S. pneumoniae* which represent at least 85% to 90% of the serotypes that cause invasive pneumococcal infections.[15,16] This vaccine was licenced in North America in 1983 and replaced an earlier 14-valent formulation that was licenced in 1977. In case-control studies, the effectiveness of the pneumococcal vaccine in preventing invasive pneumococcal disease in HIV-negative patients ranges from 55% to 80%.[17-20] In addition, a prevalence study based on the Centers for Disease Control's (CDC) pneumococcal surveillance system demonstrated a 57% overall protective effectiveness against invasive infections caused by serotypes included in the vaccine.[10,16]

Although the effectiveness of the pneumococcal vaccine is 55% to 80% in immunocompetent patients, there are no clinical trials or case-control studies to evaluate its efficacy in immunocompromised individuals including persons with HIV infection. Based on the case-control studies by Shapiro et al.[19] and Butler et al.,[16] who analyzed their results according to immunocompetence, individuals who were considered immunocompromised (persons with anatomic or functional asplenia, dysgammaglobulinemia, sickle cell disease, hematologic malignancy, metastatic cancer, chronic renal failure, nephrotic syndrome, history of organ transplant or systemic lupus erythematosus) had a vaccine effectiveness of 21% (95% CI 0-60) and 49% (95% CI 22-67) for the two studies, respectively. Thus, we used a vaccine effectiveness of 20% for the base case analysis and varied this range according to the upper and lower limit of the 95% confidence intervals from the two studies in the sensitivity analysis.

Following pneumococcal vaccination in immunocompetent individuals, serotype-specific antibodies decline after 5-10 years; however, data concerning serologic correlates of protection are inconclusive.[10] Data from one epidemiological study suggested that the duration of protection may be 9 or more years.[16] Although there are no data with respect to the duration of vaccine effectiveness in HIV patients, there are data to suggest decreasing effectiveness of the pneumococcal vaccine in certain patient groups such as the elderly and patients with chronic illness.[21,22] In order to be conservative, we assumed a decline in the base case effectiveness of the vaccine of

20% annually for the next 5 years. Thus, the time horizon for our analysis was 5 years. Based on information form the B.C. Centre for Disease Control and B.C. Centre for Excellence for HIV/AIDS, we assumed that 20% of patients who developed pneumococcal pneumonia were treated as inpatients and 80% were treated on an outpatient basis.

Vaccine safety

Pneumococcal polysaccharide vaccine is considered safe based on results from clinical trials and post-marketing surveillance since 1977. One third of individuals receiving the vaccine will experience mild side effects such as pain, erythema or swelling at the site of injection, which may persist for 48 hours.[10] Moderate systemic reactions (fever and myalgias) and more severe reactions (induration and anaphylaxis) are rare.[10] In a recent meta-analysis of nine randomized controlled trials of pneumococcal vaccine efficacy, mild local reactions were observed in less than a third of the 7,531 patients receiving the vaccine and there were no reports of severe febrile or anaphylactic reactions.[23] To date, no neurologic reactions such as Guillian-Barre syndrome have been associated with the administration of the pneumococcal vaccine.[10] Thus, we assumed a 33% incidence of mild local reactions with the pneumococcal vaccine and these could be managed with acetaminophen and an antihistamine for 48 hours. Since serious complications due to the vaccine have not been reported, these were not included in the decision tree.

Resource utilization and cost estimates

Data were collected to determine the resources used with respect to the vaccination program, treatment of pneumococcal pneumonia on outpatient and inpatient bases, and treatment of vaccine-related side effects. These resources included: 1) doses (number and amount) of antibiotic used to treat pneumococcal pneumonia; 2) number and type of laboratory tests utilized for the diagnosis and treatment; 3) diagnostic tests, procedures and treatments related to the infection or adverse events; 4) physician consults which were initiated to manage the infection or adverse event; and 5) costs associated with administering the vaccine.

TABLE II
Results of Univariate Sensitivity Analyses

Variables	Differences in Total Treatment Costs ($)	
	Supply Prescription Strategy Minus Supply the Vaccine Strategy	Do not Vaccinate Strategy Minus the Vaccinate Strategy
Incidence of bacterial pneumonia in patients on trimethoprim-sulfamethoxazole for PCP prophylaxis	56.72 to 132.20	63.03 to 146.89
Treatment of pneumococcal pneumonia (%)		
Inpatient/Outpatient	31.04 to 487.06	34.49 to 541.17
Vaccine Effect (%)		
Effectiveness	32.54 to 405.09	49.67 to 153.57
Compliance (%)		
Filling prescription of pneumococcal vaccine	0 to 118.94	118.94
Treatment of pneumococcal disease ($)		
Inpatient care	70.57 to 124.69	78.41 to 138.55
Outpatient care	103.27 to 109.00	114.75 to 121.12
Vaccine cost ($)		
23-valent pneumococcal vaccine	104.40 to 109.65	116.00 to 121.83

The actual direct medical costs associated with the vaccination program and treatment of *S. pneumoniae* infection were evaluated. Indirect costs, such as opportunity costs to the patients for time missed from work, were not included in the analysis. All costs were estimated in 1998 Canadian dollars. Costs for resource consumption by each patient were based upon data obtained from institutional and provincial sources. Future health costs were discounted at an annual rate of 5% per year. The acquisition and delivery cost of the pneumococcal vaccine was obtained from the B.C. Centre for Disease Control. For this analysis, we only used the cost of the 23-valent pneumococcal vaccine and did not add the cost of administration of the vaccine by the physician since this fee is rarely billed to the Medical Services Plan by salaried and sessional physicians or nurses who see most patients in downtown clinics.

We assumed that patients who were managed as inpatients would have invasive pneumococcal disease, otherwise they would have been managed as outpatients. The hospital that was utilized for the determination of inpatient costs was Vancouver Hospital and Health Sciences. The Department of Health Records was consulted to determine specific admissions for pneumococcal disease in the study population. Subsequently, each of these cases was reviewed by an investigator, health resource utilization was quantified, and costs were assigned. The costs associated with treating these inpatients included those of labour and material for: 1) laboratory tests (chemistry, urinalysis, complete blood count, serum antibiotic assays, microbiological cultures) – obtained from Clinical Services Unit (CSU) - Laboratory Medicine; 2) diagnostic imaging (radiology, and nuclear medicine) – obtained from CSU - Radiology and Image Guided Therapy; and 3) nutrition services (daily meals and enteral therapy) – obtained from the Department of Logistics. Since our institution is a university-affiliated teaching hospital, many physicians are salaried while others bill the provincial Ministry of Health for service. To account for these differences, we assumed a reimbursement rate per procedure or service as outlined in the 1998 British Columbia Medical Association Guide to Fees.[24] For physician consult fees outside of the attending service (i.e., Infectious Diseases, Dermatology, Psychiatry, Neurology, Nephrology), we assumed an initial primary visit that included a full work up and two follow-up visits. Average daily costs of hospitalization and nursing labour were calculated for each medical service by taking total yearly clinical care expenditures by ward and dividing this value by the number of patient days for this same period. These costs were applied to the patient depending upon the length of time spent in the various medical services.

Sensitivity analyses

Considerable uncertainty exists around several key assumptions in the model. Thus, extensive univariate and multivariate sensitivity analyses were performed to test the robustness of the model using probabilities and costs for the vaccination program, treatment of *S. pneumoniae* and treatment of vaccine-related side effects. In addition, extreme scenario analyses were conducted to determine the worst-case and base-case estimates for the model.[25] The various ranges in the sensitivity analysis were 95% confidence intervals where available. In the absence of 95% confidence intervals, a range sufficiently broad was chosen to be certain that the true value would be contained.

RESULTS

Base-case analysis

Under base-case conditions, the lowest average cost per treatment course associated with the three vaccination strategies was for directly administering the vaccine at the clinic ($595). The other two strategies were associated with a similar average cost, $702 for supplying a prescription and $714 for not vaccinating. Thus, the strategy of direct immunization in the clinic results in a reduction of over $100 in direct medical costs per patient. Therefore, for the cohort of 5,000 street-involved, HIV patients, administering the vaccine in the clinic results in a cost savings of $535,000 and $595,000 in direct medical costs to the B.C. Ministry of Health over five years when compared to the other two strategies, respectively.

In addition, not only was the direct vaccination strategy the least costly of the three, it also resulted in a reduction in episodes of pneumococcal disease, thus making it the dominant strategy. For a cohort of 5,000 HIV-positive individuals, administering the vaccine in the clinic prevents 269 and 299 additional cases of pneumococcal pneumonia when compared to giving patients a prescription for the pneumococcal vaccine and to not vaccinating HIV-positive patients, respectively.

Univariate sensitivity and break-even analyses

Extensive sensitivity and break-even analyses were performed around the parameters listed in Table I using the ranges also specified in this table. The results of select univariate sensitivity analyses have been shown in Table II. No clinically plausible changes in probability or cost estimates influenced the outcome of the model. In our extreme scenario analyses, the model in which the highest values were used resulted in a much higher cost savings and greater effect for the direct vaccination strategy (cost savings up to $5,607 per patient over the no-vaccination strategy). However, in the model utilizing the lowest values including a vaccine effectiveness of zero, the no-vaccination strategy was $6 per patient less costly than the direct vaccination strategy.

DISCUSSION

A number of studies have now shown that HIV-infected patients have a higher incidence of *S. pneumoniae* pneumonia and bacteremia than the general population.[2-8] Because carriage of *S. pneumoniae* is common in the community, there is no effective way to reduce exposure to this organism and, therefore, the Advisory Committee on Immunization Practices (ACIP) recommends administering a single dose of the 23-valent polysaccharide pneumococcal vaccine after the HIV infection is diagnosed as a preventive measure.[10] Although the ACIP recommends using the pneumococcal vaccine in all persons with HIV, there are no clinical data on the efficacy or cost-effectiveness of the vaccine in preventing invasive disease in this particular patient population.

Studies carried out in the province of Quebec indicate that privately funded immunization programs achieve a low immunization rate.[26,27] Based on this, the National Advisory Committee on Immunization (NACI) suggested using publicly funded immunization programs in Canada to decrease the burden of illness attributable to pneumococcal disease in all high-risk groups, including those living with HIV disease.[28] They also recommended that each province and territory purchase sufficient vaccine for this purpose.

A number of studies have found the use of the pneumococcal vaccine to be cost-effective in HIV-negative patients,[29-33] however, there are only two studies that have evaluated its cost-effectiveness in HIV patients.[27,34] Our study is the first in North America to evaluate the cost-effectiveness of routinely immunizing street-involved, HIV patients. Due to multiple challenges, this patient population is typically not on HAART therapy which is known to reduce the incidence of bacterial and opportunistic infections.

In both the base-case analysis and in sensitivity analyses carrying all feasible variations in assumptions, the strategy of direct provision of vaccine to street-involved people living with HIV proved most cost-effective.

Decision analysis-based models can be criticized when applied to communicable diseases because by focussing on individual outcomes, they may not factor in the effects of reduced transmission of a pathogen to others. It is not known whether immunization in this population would reduce pneumococcal carriage and lead to a degree of herd immunity. However, any bias from not evaluating this impact would be conservative.

Another factor, which could increase the cost-effectiveness of this strategy, would be the likely scenario of increasing antimicrobial resistance among pneumococci. Resistance to antibiotic therapy would be expected to increase the morbidity and costs of treatment associated with invasive pneumococcal disease and hence increase the savings associated with the prevention of such sequelae.

These findings may not be generalizable from the setting of publicly funded health care in Canada. If one body is responsible for immunization costs while another bears the costs of hospital care, there may remain a conflict in applying these results. However, in the context of publicly funded health care in Canada, the implications of these findings are clear. Recommendations for target populations for this vaccine do not require alteration. However, the process by which a publicly funded health care system assures that vaccine is delivered to those with an indication must be carefully scrutinized. If the major route of vaccine availability for street-involved people fails to achieve a high rate of immunization (as appears to be the case with the prescription-

based system), not only will people suffer excess morbidity, but also the net costs to the public of funding the health care system will increase. Were a consistent effort at direct clinic delivery of vaccine to street-involved people with HIV made, this analysis predicts that costs involved in supplying the vaccine would be more than recouped in savings attributed to lower costs for managing acute disease. There is no conflict between best practice for pneumococcal immunization and cost containment in a publicly funded health care system.

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