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Major Article

Standing orders program of pneumococcal vaccination for hospitalized elderly patients in Hong Kong: A cost-effectiveness analysis

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Key Words:
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Background: Clinical studies support a standing orders program (SOP) to improve vaccine uptake. We aimed to examine the potential cost-effectiveness of a pneumococcal vaccination SOP for Hong Kong elderly in a hospital setting.
Methods: A decision-analytic model was designed to compare the outcomes of inpatients 65 years of age or older who were eligible for pneumococcal vaccination. Two vaccination approaches were evaluated: (1) vaccination SOP, and (2) no program (control group). Outcome measures included direct medical costs, invasive pneumococcal disease–associated mortality rates, quality-adjusted life year (QALY) losses, and incremental cost per QALY saved (ICER).
Results: In the base-case analysis, mortality and QALY losses were lower and costs were higher in the SOP group when compared to the control group. The base-case ICER of the SOP group was $59,762 (all dollar amounts are in US$) per QALY saved. One-way sensitivity analyses found ICER to be sensitive to the probability of invasive pneumococcal disease among the unvaccinated elderly. Using 1× the gross domestic product per capita of Hong Kong ($43,497) and the United States ($150,000) as willingness-to-pay thresholds, SOPs were the preferred option in 37.2% and 97.5% of 10,000 Monte Carlo simulations, respectively.
Conclusions: The pneumococcal vaccination SOP for hospitalized elderly patients appeared to reduce QALY losses at a higher cost. The cost-effective acceptance of SOPs is highly dependent on the willingness-to-pay threshold.

BACKGROUND

Streptococcus pneumoniae causes a wide range of pneumococcal infections, including invasive (bacteremia and meningitis) and noninvasive (pneumonia and acute otitis media) diseases.[1] In Hong Kong, the annual incidence of invasive pneumococcal disease has increased from 1.7 per 100,000 in 2007 to 2.9 per 100,000 in 2015.[2] Of all invasive pneumococcal disease cases in 2018, 40% occurred in patients 65 years or older.[3–5]

The efficacy of pneumococcal vaccines, including the 23-valent pneumococcal polysaccharide vaccine and 13-valent pneumococcal conjugate vaccine, against pneumococcal infections in adults 65 years and older has been well demonstrated in meta-analyses and large randomized clinical trials.[6,7] The Government of the Hong Kong Special Administrative Region provides a subsidy for 1 dose of 23-valent pneumococcal polysaccharide vaccine to adults who are ≥65 years of age and have not received any pneumococcal vaccination. Despite the subsidy program, the vaccine coverage rate was only 34% in 2016, and it was much lower than the Healthy People 2020 goal of 90% coverage among elderly persons.[4,8,9]

Adult vaccinations in an inpatient setting offer an unexplored opportunity to enhance the rate of vaccination in Hong Kong. The standing orders program (SOP) of vaccination authorizes health care

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professional staff such as pharmacists and nurses to assess patient eligibility and administer vaccines without a physician's order. Because clinical studies have reported that the SOP has improved the vaccination coverage rate,[10–15] SOPs have the potential to be cost-effective measures to maximize the clinical benefit of pneumococcal vaccination among the elderly in Hong Kong. In the present study, we aimed to examine the potential costs and clinical outcomes of pneumococcal vaccination SOPs for the Hong Kong elderly in a hospital setting from the perspective of public health care providers.

METHODS

Model design

A Markov model (Fig 1) was designed to compare the outcomes of a hypothetical cohort of inpatients who were ≥65 years of age, were eligible for the 23-valent pneumococcal polysaccharide vaccine,[8] and did not have contraindications to the pneumococcal vaccine at the time of discharge from a Hong Kong public hospital. Two vaccination approaches were evaluated: (1) pneumococcal vaccination SOP, and (2) no program (control group). Markov modeling is a form of decision analysis in which hypothetical patients proceed through different Markov health states in every model cycle over time. The transition between health states was based on probability inputs of the model, and the time horizon of the model was 10 years with a yearly cycle length. The model outcomes included direct medical costs, invasive pneumococcal disease–associated mortality rates, and quality-adjusted life year (QALY) loss.

In the SOP arm, a non-physician health care professional (SOP staff), either a nurse or pharmacist, evaluated the eligibility of hospitalized patients for pneumococcal vaccination (including history of vaccination and contraindications to the vaccine). The SOP staff further provided pneumococcal vaccination information to the eligible patients or their caregivers, who might or might not agree to receive the vaccine. If the eligible patients or their caregivers agreed to receive the pneumococcal vaccination, the SOP staff administered the vaccine before the eligible patients were discharged. The most commonly reported adverse event related to the 23-valent pneumococcal polysaccharide vaccine was minor injection site reactions; therefore, the costs and outcomes of vaccine-associated adverse events were not included in the model. In the control group, no pneumococcal vaccination was offered during the hospital stay.

It should be noted that in each yearly cycle both vaccinated and unvaccinated patients might die of all causes. People might or might not acquire invasive pneumococcal disease, and infected patients might survive or die with or without admission to an intensive care unit.

Clinical inputs

The model parameters are listed in Table 1. A literature search was performed on MEDLINE from 2000 to 2018 with the key words "pneumococcal infection," "pneumonia," "invasive pneumococcal disease," "aged," "23-valent pneumococcal polysaccharide vaccine," "vaccine effectiveness," "clinical outcomes," "mortality," "intensive care unit," and "critical care." The published articles retrieved were screened for relevance to the present model, and case reports were excluded. Meta-analyses and randomized controlled trials were the preferred types of studies. For variables reported in multiple studies, a weighted average was used as the base-case value, and the highest and lowest values were the range used for sensitivity analysis.

The Hospital Authority is a statutory body responsible for the management of public hospitals in Hong Kong. According to the Hospital Authority Statistical Report 2016-2017, the 75 years or older age group had higher discharges (368,440) than the group of patients 65 to 74 years of age (156,861).[16] The age of 75 years was therefore used as the base-case value of the hypothetical cohort of elderly patients, and the range of 65 to 85 years was used as the range for sensitivity analysis.

The model used the yearly vaccine effectiveness of the 23-valent pneumococcal polysaccharide vaccine against invasive pneumococcal disease in years 1 to 10, as previously derived in 2 cost-effectiveness studies of pneumococcal vaccination, and a vaccine effectiveness adjustment factor of ±10% was incorporated to represent individual variation.[17,18] The vaccination rate in the SOP group was estimated from the weighted average of SOP vaccine uptake rates for adult vaccination in 2 outcome studies (70.0%; range, 69%-74%).[13,19]

The annual incidence in Hong Kong of invasive pneumococcal disease among adults ≥ 65 years of age (8.3 per 100,000) was estimated from invasive pneumococcal disease cases reported by The Centre for Health Protection and from the age-specific population of Hong Kong in 2018.[20,21] The range of invasive pneumococcal disease incidence (2.6/100,000 to 12.4/100,000) and the mortality rate of invasive pneumococcal disease in the inpatient setting (0.16; range, 0.082-

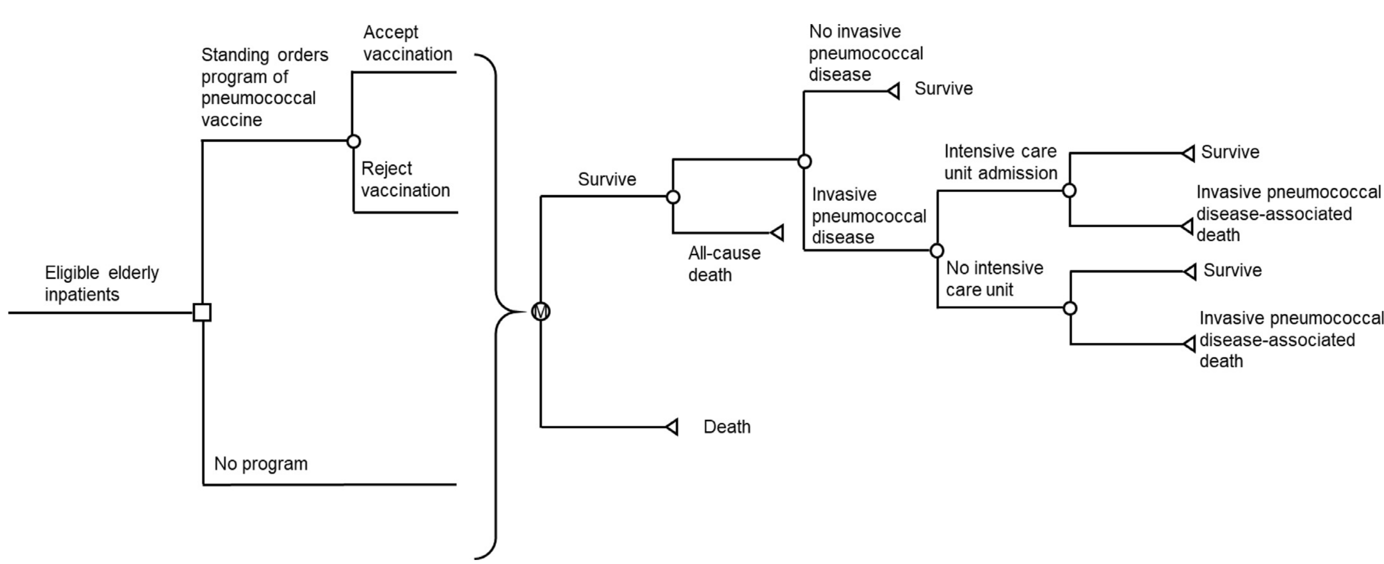

Fig 1. Simplified decision-analytic model of a standing orders program for pneumococcal vaccination versus no program for hospitalized elderly patients.

Table 1
Model inputs

Variables	Base-case value	Range	Distribution type	References
Clinical inputs				
Age (y)	75	65-85	Triangular	16
Vaccine effectiveness				17
Year 1	0.82	—	—	
Year 2	0.78	—	—	
Year 3	0.72	—	—	
Year 4	0.64	—	—	
Year 5	0.54	—	—	
Year 6	0.43	—	—	
Year 7	0.3	—	—	
Year 8	0.15	—	—	
Year 9	0	—	—	
Year 10	0	—	—	
Vaccine effectiveness adjusting factor	1	0.9-1.1	Triangular	17, 18
Vaccine acceptance rate in standing orders program	0.70	0.69-0.74	Beta	13, 19
Probability of invasive pneumococcal disease in unvaccinated patients	0.000083	0.000026-0.000124	Beta	20-22
Intensive care unit admission	0.221	0.188-0.261	Beta	23
Mortality				
All-cause	0.02665	0.009-0.109	Beta	27
Invasive pneumococcal disease−associated death	0.16	0.082-0.187	Beta	22
Invasive pneumococcal disease−associated death in intensive care unit	0.238	0.18-0.28	Beta	24-26
Length of stay for invasive pneumococcal disease (d)				28
Hospitalization	13	10.3-15.8	Uniform	
Intensive care unit	2.4	0.9-4.2	Uniform	
Utility inputs				
Utility of age ≥ 65 y	0.84	—	—	29
Utility of invasive pneumococcal disease	0.2	0.15-0.25	Triangular	30
Utility of invasive pneumococcal disease in intensive care unit	0.1	0.075-0.125	Triangular	—*
Cost inputs (USD)				
Intensive care unit per day	3128	—	—	31
Hospitalization per day	654	—	—	31
Standing orders program	5	4-6	Triangular	13, 32, 33
Pneumococcal vaccine	32	10-38	Triangular	—†

*Assumption.
†Local pricing.

0.187) were derived from the findings of a population-based epidemiology study on the National Health Insurance Research Database in Taiwan.[22] The intensive care unit admission rate for invasive pneumococcal disease (0.221; range, 0.188-0.261) was retrieved from a retrospective cohort study on surveillance data of hospitalized patients in the Netherlands.[23] Invasive pneumococcal disease mortality in intensive care units (0.238; range 0.18-0.28) was based on a study that assessed the epidemiological and economic burdens of pneumococcal infections and on 2 outcome studies of severe pneumococcal infections in intensive care units.[24−26] The all-cause mortality rate was based on statistics reported by the latest version of Mortality Trend in Hong Kong; the mortality rates of adults ages 75 to 79 years were used as the base-case values, and the mortality rates of adults ≥ 85 years of age and adults 65 to 69 years of age were used as the high and low values, respectively.[27] The lengths of stay for intensive care (2.4 days; range, 0.9-4.2 days) and hospitalization (13 days; range, 10.3-15.8 day) due to invasive pneumococcal disease were approximated from an observational study of hospitalization costs for pneumonia among the Dutch elderly.[28]

Utility and cost inputs

The QALY loss of each patient with invasive pneumococcal disease was calculated based on loss of utility and (1) duration of time spent in a non-intensive care unit care for invasive pneumococcal disease, (2) duration of time spent in an intensive care unit care for invasive pneumococcal disease, or (3) death associated with invasive pneumococcal disease. The loss of utility due to invasive pneumococcal disease was estimated from the difference between the age-specific utility value of the ≥65-year-old cohort (0.84) and the utility value of invasive pneumococcal disease (0.2; range 0.15-0.25).[29,30] The utility value of an intensive care unit stay was assumed to be half that of a non-intensive care unit stay; therefore, the utility value of invasive pneumococcal disease treated in an intensive care unit was reduced by 50%. The QALY loss as a result of death associated with invasive pneumococcal disease was calculated using the Hong Kong life expectancy and age-specific utility values.[21,29]

The economic analysis was conducted from the perspective of Hong Kong public health care providers, and direct medical costs were included. The cost per day of treatment in an intensive care unit was $3128 (all dollar amounts are in US$), and the cost per day in a medical ward was $654, as derived from 2019 charges for non-eligible persons under the Hospital Authority,[31] which is subsidized by the Government of the Hong Kong Special Administrative Region. The charges listed for non-residents of Hong Kong were assumed to include only the components of costs (including labor costs) and no profit margins, and they were used to estimate health service costs. The SOP included screening of patients eligible for the 23-valent pneumococcal polysaccharide vaccine and providing education to the identified patients. The SOP cost per eligible patient was $5 (range, $4-$6), calculated based on the median wages of nurses and pharmacists from the Hospital Authority[32] and the time required for screening and education. The time spent on each patient was estimated to be 10 minutes, based on the findings of a SOP implementation study in the United States and a clinical trial of health education on vaccination in Hong Kong.[13,33] The cost of the 23-valent pneumococcal polysaccharide vaccine ($32) was based on local pricing. Both cumulative cost and QALY loss in this 10-year model were discounted to the year 2019 by an annual rate of 3%.

Cost-effectiveness and sensitivity analyses

The expected direct medical costs, mortality rates associated with invasive pneumococcal disease, and QALY losses were simulated using the base-case model input values. If the SOP cost more to save QALYs, then the incremental cost per QALY saved (ICER) by the SOP was calculated as follows:

$$ICER = (Cost_{SOP} - Cost_{Control})/(QALY\ loss_{Control} - QALY\ loss_{SOP})$$

In 2017, the gross domestic product per capita of Hong Kong was $46,153.[34] As recommended by the World Health Organization, an ICER value less than 3× the gross domestic product per capita was considered to be cost effective. We therefore adopted $138,460 (3× gross domestic product per capita) as the willingness-to-pay threshold for cost-effective SOP interventions.

Base-case and sensitivity analyses were performed by TreeAge Pro 2009 (TreeAge Software, Inc; Williamstown, MA) and Microsoft Excel 2013 (Microsoft Corporation; Redmond, WA). One-way sensitivity analyses that varied all model inputs were performed for each model outcome (cost, invasive pneumococcal disease–associated mortality, and QALY loss) to identify influential factors with threshold values. The probabilistic sensitivity analyses were performed using Monte Carlo simulation. The direct costs and QALY losses of each study arm were recalculated 10,000 times by randomly drawing each of the model inputs from a specified probability distribution. The probability of each study arm to be the preferred option was determined over a wide range of willingness-to-pay thresholds ($0 to $150,000).

RESULTS

Base-case analysis

In the base-case analysis, invasive pneumococcal disease–associated mortality for the SOP group was 0.010 per 100 patients eligible for pneumococcal vaccination, compared to 0.014 for the control group. QALY losses in the SOP group were 0.00099 compared to 0.00141 in the control group; however, the lower value in the SOP group came at a higher cost ($33.00 vs $7.90). The base-case ICER of the SOP group was $59,762 per QALY saved.

Sensitivity analysis

One-way sensitivity analyses found that mortality and QALY losses were lower but costs were higher in the SOP group compared to the control group throughout all model input variations. The impact of each model input on the ICER of the SOP group is shown in a tornado diagram in Figure 2. The probability of invasive pneumococcal disease among unvaccinated elderly was the most influential parameter on the ICER of the SOP group. The ICER became higher than the willingness-to-pay threshold ($138,460) when the probability of invasive pneumococcal disease fell below 0.000038 (3.8 in 100,000). Costs, QALY losses, and the probability of invasive pneumococcal disease among unvaccinated elderly are illustrated in Figure 3.

In the 10,000 Monte Carlo simulations generated by probabilistic sensitivity analyses, the SOP group cost more than the control group by $21.30 (95% confidence interval, 21.20-21.40; $P < .001$) and saved 0.000418 QALYs (95% confidence interval, 0.000414-0.000421; $P < .001$). The ICERs of the SOP group were below the willingness-to-pay threshold in 96.6% of the 10,000 simulations. The probabilities of SOP being the preferred option were evaluated based on acceptability curves over a wide willingness-to-pay range ($0-$150,000) (Fig 4). The SOP was the preferred option in 37.2% of 10,000 Monte Carlo simulations when 1× gross domestic product per capita ($43,497) was used as the willingness-to-pay threshold. The probability of SOP to be preferred increased to 97.5% when the willingness-to-pay threshold was $150,000.

DISCUSSION

The present study examined the cost-effectiveness of a SOP for the 23-valent pneumococcal polysaccharide vaccine for hospitalized elderly patients eligible for discharge from a public health care provider in Hong Kong. The base-case analysis results showed that the SOP intervention reduced invasive pneumococcal disease–associated mortality and QALY losses at a higher cost as compared to the scenario without the SOP. The one-way sensitivity analysis found that the base-case analysis results of higher costs in the SOP group to reduce invasive pneumococcal disease–associated mortality and QALY losses were highly robust.

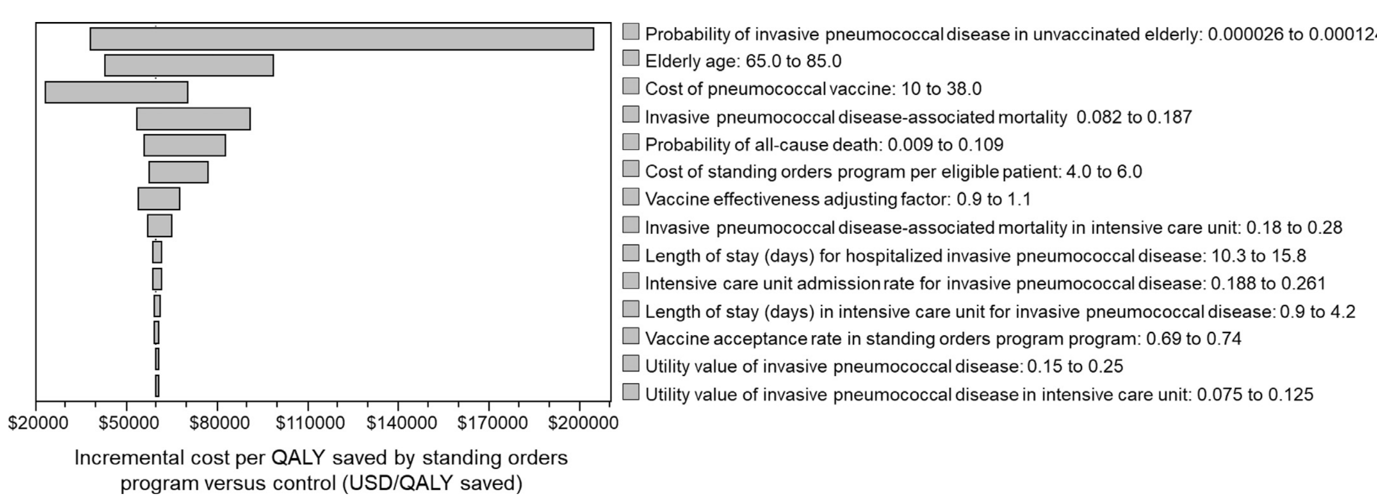

Fig 2. One-way sensitivity analysis (tornado diagram) of all parameters on ICER of a standing orders program versus no program (control). *ICER*, incremental cost per QALY saved; *QALY*, quality-adjusted life year; *USD*, US dollars.

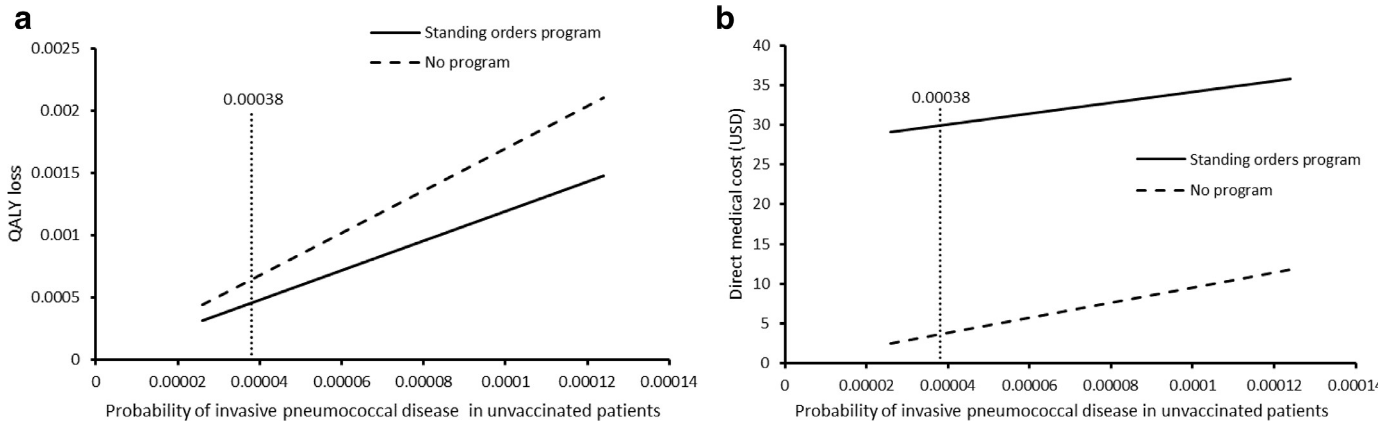

Fig 3. One-way sensitivity analysis of (a) QALY loss and (b) direct medical cost against probability of invasive pneumococcal disease in unvaccinated elderly. *QALY*, quality-adjusted life year; *USD*, US dollars.

The ICER of the SOP was sensitive to the probability of invasive pneumococcal disease in unvaccinated elderly. When the probability of invasive pneumococcal disease decreased from the base-case value (0.000083), the difference in QALY losses between the 2 study arms narrowed while the difference in costs between the 2 groups broadened. Due to the higher incremental costs associated with reducing the probability of invasive pneumococcal disease, the ICER of the SOP increased and exceeded the willingness-to-pay threshold when the probability of invasive pneumococcal disease was lower than 0.000038. The robustness of the base-case results was further supported by probabilistic sensitivity analysis showing that the SOP saved QALYs at a higher cost in 100% of 10,000 Monte Carlo simulations.

These findings are similar to the results of a US cost-effectiveness analysis of a SOP for pneumococcal polysaccharide vaccine vaccination which found that the SOP saved QALYs at higher costs in the hospital setting.[17] Nevertheless, the base-case ICER in our analysis ($59,762 per QALY) was higher than the ICERs ($2432-$8859 per QALY) in the US hospital setting. The incidence rates of invasive pneumococcal disease in populations ages 65 years to ≥85 years have ranged from 20.1 to 93.2 cases per 100,000 in prior US analyses and are higher than the invasive pneumococcal disease incidence rates in Hong Kong (base-case value, 8.3; range, 2.6-12.4 per 100,000), which were applied in our model. As indicated by the one-way sensitivity analysis, the probability of

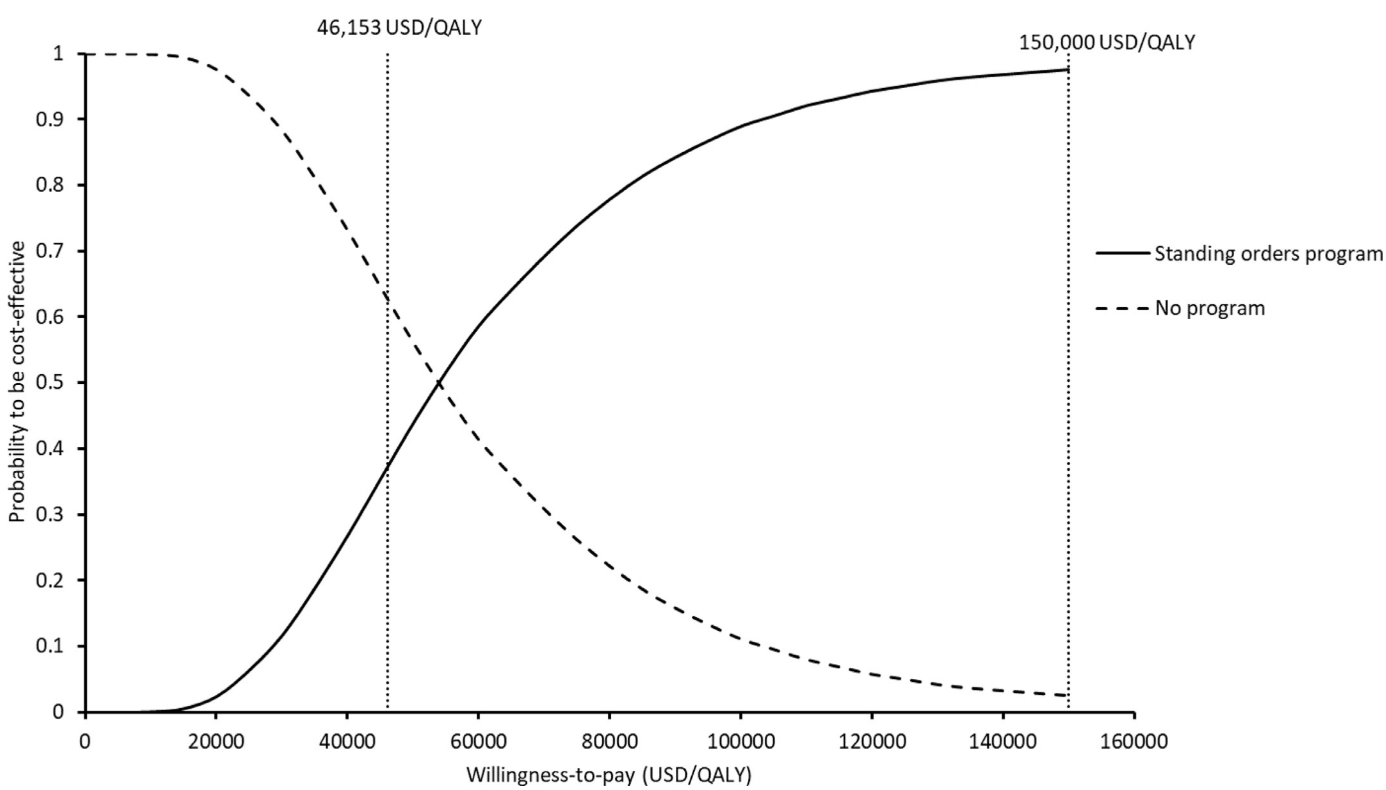

Fig 4. Acceptability curves of a SOP and no program versus willingness to pay. *QALY*, quality-adjusted life year; *SOP*, standing orders program; *USD*, US dollars.

invasive pneumococcal disease influenced ICER values. When a higher probability of invasive pneumococcal disease (>35 cases per 100,000) was applied to the model, the ICER of the SOP declined to <$10,000 per QALY (data not shown).

This is the first cost-effectiveness analysis of a pneumococcal vaccination SOP in a Hong Kong hospital setting. According to the US Centers for Disease Control and Prevention, over 65% of patients admitted for severe pneumococcal infection have had a history of prior hospitalization for other conditions within the past 3 to 5 years,[9] a finding that supports screening eligible hospitalized patients and offering pneumococcal vaccination when appropriate. The effectiveness of SOPs on vaccination coverage rates has been demonstrated in multiple trials,[10−15] and our study results provide further evidence of the economic importance of SOPs for pneumococcal vaccination in Hong Kong. The vaccine subsidy program for pneumococcal vaccination in Hong Kong supports the full price of vaccination, yet the vaccine uptake rate has been only 34%.[4,8] The findings of this study should encourage Hong Kong health care providers and public health administrators to improve SOP vaccine coverage among eligible elderly patients in a hospital setting. Our model also provides a decision-analytic framework to evaluate SOPs for vaccination programs in institutionalized settings such as rehabilitation and long-term care facilities.

Our analysis was limited by uncertainty regarding the model inputs, as well as simplification of real-life events. A few clinical inputs (mortality rate and intensive care unit admission rate for invasive pneumococcal disease) were not available for Hong Kong and were adopted from other regions. The borrowed statistics from overseas might result in under- or overestimation of the invasive pneumococcal disease burden in Hong Kong and the corresponding impact of SOPs. Sensitivity analyses on all model inputs were therefore conducted to examine the robustness of the base-case results. Adverse events associated with the 23-valent pneumococcal polysaccharide vaccine were not included in the model, as minor injection site reaction was the most commonly reported event, so the costs and QALY losses associated with vaccination might be underestimated. Only direct medical costs were included in the economic analysis, and the indirect costs associated with invasive pneumococcal disease (such as the costs of caregivers) were not evaluated. The results might therefore underestimate the economic benefits of the SOP from the societal perspective of Hong Kong.

CONCLUSIONS

The SOP of 23-valent pneumococcal polysaccharide vaccine for hospitalized elderly patients appeared to reduce invasive pneumococcal disease−associated QALY losses but at a higher cost when compared to no program. Acceptance of cost-effective SOPs is subject to the incidence of invasive pneumococcal disease among the elderly population and the willingness-to-pay threshold.

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