Cost-effectiveness of influenza immunization in adult cancer patients in Taiwan

H-H. Lin[1], K-L. Hsu[1], W. W-C. Ko[2], Y-C. Yang[3], Y-W. Chang[1], M-C. Yu[4] and K-T. Chen[1]

1) *Department of Public Health,* 2) *Division of Infectious Diseases, Department of Internal Medicine,* 3) *Department of Family Medicine, College of Medicine, National Cheng Kung University, Tainan, Taiwan and* 4) *Department of Chemical Engineering, Tatung University, Taipai, Taiwan*

Abstract

The aim of this study was to investigate the efficacy of the influenza vaccine among cancer patients in Taiwan. We determined the effect of immunization on the following outcomes of disease: hospitalizations, emergency department visits, hospital outpatient visits, physician office visits, and deaths. Cost-effectiveness was analysed from the perspectives of the healthcare system and society. A decision tree was used, with estimates of disease burden and costs based on data from published and unpublished sources. The model followed 34 112 cancer patients aged 20–64 years who were registered by the Taiwan National Cancer Registry in 2002. An influenza immunization programme for the cancer population would prevent 2555 cases of all types of influenza infection, 660 of which would be serious cases involving hospitalization, emergency department visits and death. From the perspective of the healthcare system, the programme would cost US$7.7 million, providing net savings of US$5.4 million. From a societal perspective, the programme would cost US$28.6 million, providing net savings of US$22.3 million. This corresponds to savings of US$2107 and US$6338 per case averted, from healthcare and societal perspectives, respectively, as well as 110 lives saved. Lesser disease burden, greater vaccine efficacy and lower cost of hospitalizations increased cost-effectiveness. Influenza immunization for cancer patients is cost-saving and cost-effective from a healthcare and societal perspective in Taiwan. We highly recommend annual influenza vaccinations for this patient group.

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Corresponding author and reprint requests: Dr. K-T. Chen, Department of Public Health, College of Medicine, National Cheng-Kung University, Taiwan. No. 1, University Road, Tainan, Taiwan
E-mail: ktchen@mail.ncku.edu.tw

Introduction

Influenza infection is a major cause of morbidity and mortality around the world. Between 1% and 26% of persons aged 18–64 years may be infected with influenza annually [1–3], and the associated work absenteeism results in substantial societal cost [4,5]. The effectiveness of inactivated influenza vaccination in reducing influenza illness, hospitalization and death is well established for healthy working adults and persons aged ≥65 years, a group that is at increased risk of severe influenza-related complications [6,7].

Cancer patients are another group that is at increased risk of both contracting influenza and experiencing severe complications. Several studies have shown an increased incidence and duration of influenza infection among cancer patients [8–10]. Also, influenza-related infections in cancer patients have been associated with costly hospitalizations, delays in potentially life-saving therapy, and death [11,12].

In the USA, recommendations are in place to immunize all patients at risk of complications from influenza. Despite these recommendations and the availability of a suitable vaccine, the rate of vaccination among all high-risk adults aged 18–64 years is only 35% [13]. In a surveillance study focused exclusively on cancer patients, non-elderly adult cancer patients also had a low rate of influenza immunization (17%) [14]. Importantly, the low rates of influenza vaccination among cancer patients in particular may be influenced by controversy over the effectiveness of the vaccine in this high-risk subpopulation [15]. Evidence suggests that even though cancer patients' immune response to influenza vaccination might be attenuated, vaccination can still protect against influenza infection [16]. Indeed, the influenza vaccine was found to be cost-effective for working-age cancer patients with a life expectancy of >3 months [10,17]. In Taiwan immunization is recommended for all patients at increased risk of influenza complications [18]. However, vaccine utilization among cancer patients and its cost-effectiveness remain unclear. Therefore, we analysed the cost-effectiveness of influenza vaccination in adults, aged 20–64 years, who are at increased risk of influenza-related complications due to underlying malignancy.

Methods

Study design

A decision model was used to calculate total costs and estimate health outcomes (influenza infection, physician and emergency department visits, hospitalizations, and deaths) associated with influenza infections in cancer patients aged 20–64 years (Fig. 1). We calculated both incremental costs (the ratio of the costs divided by the number of cases of influenza infection prevented by an immunization programme) and lives saved. Cost-effectiveness was analysed from two perspectives: (i) that of the healthcare system, which includes medical costs associated with influenza infections and the immunization programme, and (ii) that of society, which includes medical and non-medical costs. Non-medical costs included lost workdays and lost lifetime productivity from complication-induced death. Parameters for our decision tree were derived from published and unpublished papers on the effectiveness of influenza vaccination, as well as resource utilities and cost of hospitalizations among cancer patients.

The time horizon for risk of influenza infection, protection from the vaccine, and cost of vaccination parameters was 1 year, because vaccination must be repeated annually due to changes in the influenza virus structure year to year. The model followed 34 112 cancer patients between 20 and 64 years of age from the Taiwan National Cancer Registry in 2002.

Costs and wages published before 2007 were updated using the consumer price index. Future disease costs and influenza cases were modelled at an annual discount rate of 3%. The medical costs of influenza cases occurring over a 1-year period were calculated according to the age-specific incidence estimates for each outcome. Productivity costs associated with influenza-related mortality were estimated for the average life expectancy of cancer patients younger than 65 years. All costs are expressed in 2007 US dollars. The monetary values in New Taiwan dollars (NT) were converted into US dollars (US$) based on the average exchange rate in 2007 (1 US$ = 31.0 NT$).

Data source

The Taiwanese government implemented a mandatory national health insurance programme in 1995. By 1999, approximately 96% of Taiwan's population was covered by the programme [19], which provides comprehensive coverage including inpatient care, ambulatory care, laboratory

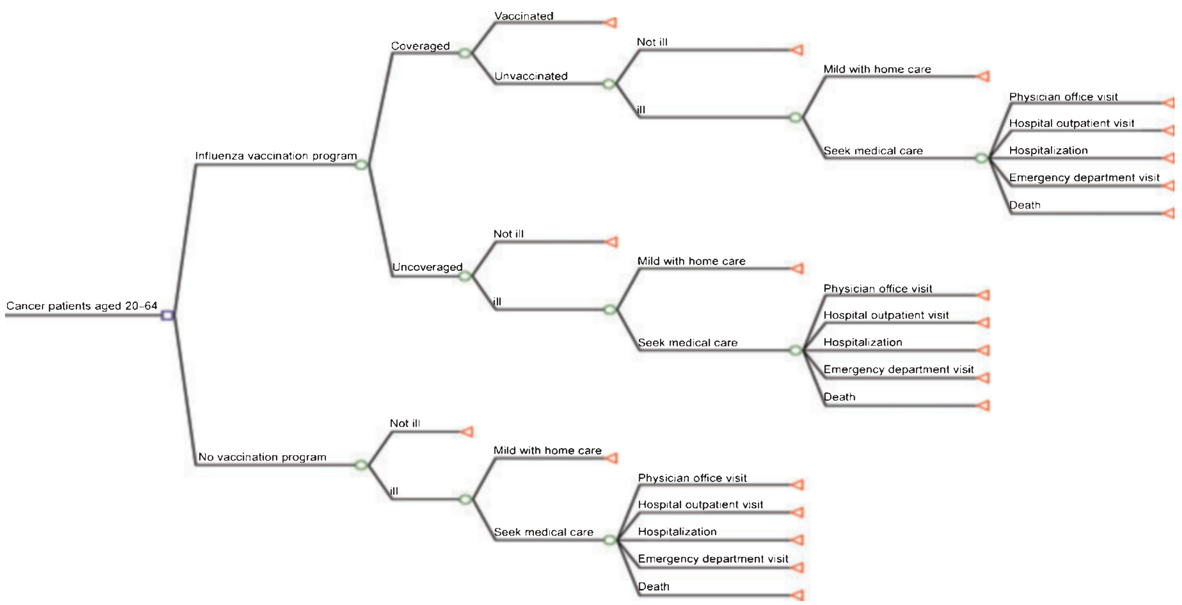

FIG. 1. Decision tree for an influenza immunization programme in Taiwan. The programme with no vaccination is compared with vaccination programmes in which influenza vaccine is included in a national adult cancer patient immunization programme.

tests, prescription drugs and certain non-prescription drugs, dental services, traditional Chinese medicine, and certain preventative services. A co-payment is required for ambulatory care, inpatient care, and pharmaceuticals. No co-payment is required of low-income households or veterans, or for services relating to catastrophic diseases, child birth, or preventative healthcare. Medical services in particular mountainous areas and offshore islands are also exempt from co-payment.

We obtained data on hospitalization, outpatient and emergency department visits from the National Health Insurance Report (NHIR) for 1998 to 2002. The NHIR database contains all medical claims records (inpatient and outpatient care) and includes information on ID number, gender, birth date, date of visit, length of hospital stay (LOS), and International Classification of Disease (ICD). The ICD used was the Ninth Revision, and Clinical Modification (ICD-9-CM) diagnosis (ICD-9 CM easy coder 2002) and the major disease classification included neoplasm (ICD-9-CM code, 140-239). We applied the ICD-9-CM respiratory illness-associated diagnosis codes for acute respiratory infections of determined causes: pneumonia and influenza (480-487), chronic obstructive pulmonary disease (490-496), and other diseases (510-519). All events were regarded as discrete episodes even if patients had been treated for influenza on more than one occasion.

Information about cancer, including the date of diagnosis, was obtained from the Cancer Registry of Taiwan, a population-based registry opened in 1979. Registry-trained personnel review all discharge notes and all data concerning patients' primary diagnosis of cancer. Notifications of deaths from cancer in hospitals housing at least 30 beds are forwarded to the National Health Department of Taiwan on a voluntary basis. Almost all such hospitals (at least 142) participate in this cancer registry. The data from this registry have passed rigorous quality assurance checks, including a completeness estimate of case ascertainment of >90% [20].

Decision analysis

We compared influenza-related disease outcomes with and without an immunization programme using a decision-tree model with the TreeAge Pro decision analysis software (TreeAge pro healthcare 2007; TreeAge Software Inc., Williamstown, MA, USA). We analysed the decision tree to determine the costs of two options: inactivated influenza vaccination and no influenza vaccination.

Estimates of disease burden of influenza infection

We estimated the probability of influenza infections based on published data from Chemaly's study [21], in which approximately 18% of leukaemia patients ≥17 years old were followed for acute respiratory illness between 2000 and 2002.

Annual national weighted estimates of the mean total number of influenza infection episodes requiring care among cancer patients aged 20–64 years were obtained from the NHIR database, covering years 1998 to 2002 [19]. The probabilities of hospitalization, outpatient visits and emergency department visits were based on estimates of annual national cases of influenza virus from data collected by the Taiwanese Centre for Disease Control (CDC, Taiwan). These data indicated that an influenza season typically includes the autumn and winter months (October–March) [18]. Using this definition, we included discharge records from the first (January–March) and fourth quarters (October–December) of each of the 5 years studied. We estimated influenza-related episodes among the general population using a method similar to that previously described [22,23], estimating the number of excess cases caused by influenza by subtracting the expected number of cases (based on April–September data) from total cases during the influenza season (October–March). The risk of outpatient visits (HOV), emergency department visits (EDV) and hospitalizations for influenza infections was estimated as the proportion of visits or hospitalizations for influenza that could be attributed to influenza infections (Table 1).

Rates of seeking medical care in vaccinated and unvaccinated cancer patients were estimated from published data, looking at the number of episodes of upper respiratory illness, the amount of sick leave taken, and physician visits after vaccine vs. placebo [3,4]. We used 0.45 (range 0.22–0.67) as the rate of seeking medical care for the unvaccinated group, and 0.35 (range 0.18–0.53) for vaccinated cancer patients.

TABLE 1. Model parameters: base-case values and sensitivity ranges

	Base-case	Sensitivity range	Source
Effectiveness of influenza vaccine	0.33	0.27–0.38	[8,16,24,26]
Coverage rate of influenza vaccination	0.57	0.29–0.86	[18]
Risk of influenza infection	0.18	0.09–0.27	[19,23]
Risk of seeking medical care			
Unvaccinated group	0.45	0.22–0.67	[3,4]
Resource utility	0.35	0.18–0.53	[3,4]
Risk of influenza-related hospitalization	0.32	0.16–0.48	[3,4,19]
Risk of influenza-related EDV	0.13	0.07–0.20	[3,4,19]
Risk of influenza-related HOV	0.03	0.02–0.05	[3,4,19]
Risk of influenza-related POV	0.43	0.22–0.65	[3,4,19]
Risk of influenza-related death	0.09	0.05–0.14	[3,4,19]
Labour force participation rate	0.58	0.29–0.87	[27]

EDV, emergency department visits; HOV, hospital outpatient visits; POV, physician office visits.

We estimated that 0.32 (range 0.16–0.48) of hospitalizations were associated with influenza infection. Therefore, 874 of the hospitalizations were attributable to influenza infection. We also estimated that 0.43 (range 0.22–0.65) of physician office visits (POV) and 0.03 (range 0.02–0.05) of HOV for respiratory illness were due to influenza [19,21]. Therefore, we attributed 1175 of the POV and 82 of the HOV to influenza. Similarly, we estimated that 0.13 (range 0.07–0.20) of EDV for respiratory illness were due to influenza, providing a national estimate of 355 EDV for influenza. Finally, we estimated that 0.09 (range 0.05–0.14) of the annual deaths were due to influenza infection; thus, among these cancer patients, 246 deaths annually are attributable to influenza (Table 1) [19].

Vaccine coverage estimates

Influenza vaccine coverage was based on the report from the CDC, Taiwan. We assumed that the cancer patients had the same rate of influenza vaccination as that of elderly people. In 2006, 0.57 (range 0.29–0.86) of elderly people in Taiwan received influenza vaccination [18].

Vaccine effectiveness

We obtained an estimate of the effectiveness of the influenza vaccine in cancer patients aged 20–64 years based on published studies of seroconversion in adult cancer patients after immunization with split virion influenza vaccine [8,24,25] in which the overall quality-adjusted protection rate was obtained using the bootstrap Efron [26]. This gave an estimated protection rate of 0.33 (range 0.27–0.38) for influenza immunization (Table 1).

Cost estimates

Medical costs were determined by combining costs of inpatient, outpatient and emergency department care, as well as costs associated with vaccination (Table 2). The cost of hospitalization included the daily room charge, inpatient physician visits, medications, intravenous fluids, laboratory tests, and one post-discharge outpatient visit. The cost of an outpatient visit, including laboratory tests and medications, was derived from the data of the NHIR, Taiwan [19] and was consistent with current published costs [12]. From this report, we also obtained the cost of a regular emergency department visit, the cost of treatment for a dying adult, including ambulance transportation and 30 min of critical care in an emergency department, and the cost of influenza vaccine administration [19]. Finally, the costs of pharmaceuticals and inactivated influenza vaccine were based on the pharmaceutical industry's average wholesale price as listed in Table 2. Medical cost estimates excluding vaccine price were increased and decreased by 20% for the upper and lower limits, respectively, in the sensitivity test analysis.

The non-medical costs of an episode of influenza infection were travel to seek healthcare and work absenteeism. Costs associated with work absenteeism were based on the mean per capita income by age, obtained from the Taiwan Census 2007 [27,28]. These were inflated to 2007 US dollars using the general consumer price index and age-adjusted to the 5-year cancer prevalence for the Taiwan Cancer Registry population, aged 20–64 years (Table 2). We assumed that influenza-infected patients requiring hospitalization would be absent from work for the length of hospitalization, which was based on the reported mean LOS for influenza-related admissions of working-age cancer patients [11,12]. We also assumed that influenza-infected cancer patients who required an emergency visit or an office visit would be absent from work for the day.

Sensitivity analysis

Starting from the base-case scenario, we performed a univariate sensitivity analysis to examine the range of values for all variables, to reflect uncertainties in our estimates. Best and worst case scenarios were also calculated by biasing the model for and against an immunization programme, respectively, without varying the vaccine price. The vaccine price, coverage, efficacy, disease burden, medical costs, patient's life expectancy, and discount rate used in the decision tree were varied in the sensitivity analysis. Vaccination was considered to be cost-effective if the cost-effective ratio was less than three times the gross domestic product per capita, which was US$16 111 for Taiwan in 2006 [29,30].

TABLE 2. Influenza infection cost estimates in 2007 US dollars in Taiwan

	Base-case	Sensitivity range	Source
Cost of vaccine per dose	19.4	9.7–29.0	Base: ex-manufacturer price
Cost of vaccination	7.0	3.0–12.0	[19]
Direct medical costs			
Hospitalization	1724.6	862.3–2586.9	[12,19]
EDV	26.2	13.1–39.4	[19]
HOV	13.1	6.6–19.7	[19]
POV	11.5	5.7–17.2	[19]
Non-medical costs			
Average earnings/day	45.0	38.2–114.5	[27,28]

EDV, emergency department visits; HOV, hospital outpatient visits; POV, physician office visits.

Results

Base-case estimate

A total of 34 112 cancer patients, aged 20–64 years, were included to analyse the cost-effectiveness of influenza vaccination. We found that an influenza immunization programme for the cancer population would prevent 42% (2555/6140) of all cases, and 45% (660/1475) of all serious cases (hospitalizations, emergency department visits and deaths) of influenza infections (Table 3). Our analysis estimated that influenza vaccination of all cancer patients aged 20–64 years would prevent 110 deaths, 391 hospitalizations, 159 EDV, 526 POV and 37 HOV. From the perspective of healthcare, the programme would cost US$7.7 million, providing a net savings of US$5.4 million, and produce a cost savings of US$2107 per case averted.

From a societal perspective, the programme would cost US$28.6 million and provide net savings of US$22.3 million. Compared with no vaccination, the vaccination programme resulted in a saving of US$6338 per case averted (Table 3).

Sensitivity analysis

In one-way sensitivity analysis, the decision model was robust to plausible change in the values of influenza incidence, vaccine effectiveness, vaccine price, death due to influenza, risk of seeking medical care, labour force participant rate, average earnings, and costs for hospitalization (Tables 1 and 2). The most influential variable was the risk of seeking medical care for the unvaccinated group. When the risk of seeking medical care for the unvaccinated group was set at its lowest value (0.22), the incremental cost per case prevented increased to US$3548 from the healthcare system perspective and to US$14 194 from the societal perspective. When the risk of seeking medical care for the unvaccinated group was set at its highest value (0.67), the incremental cost per case prevented fell to US$640 from the healthcare system perspective and to US$2903 from the societal perspective. The other variables found to have some influence on the incremental cost ratio from the societal perspective were rate of influenza attack, vaccine coverage from the healthcare perspective, risk of death due to influenza, labour force participation rate, and average earnings (Fig. 2).

In a two-way sensitivity analysis of the rate of influenza infection and vaccine effectiveness, the rate of influenza infection was lowered to vary from 0.09 to 0.27, the annual rate of infection observed in Taiwan [18]. At the same time, vaccine effectiveness was allowed from 0.32 to 0.76 for the estimated rate of protection in cancer patients (Fig. 3).

TABLE 3. Influenza health outcomes and costs with and without an influenza immunization programme[a]

	No intervention	Vaccination	Difference
Events no.			
Total influenza infections	6140	3585	2555
No medical care	3408	2076	1332
HOV	82	45	37
POV	1175	649	526
EDV	355	196	159
Hospitalizations	874	483	391
Deaths	246	136	110
Costs, US$			
Direct medical costs	13 080 096	7 697 438	5 382 658
HOV	1473	809	664
POV	45 939	25 397	20 542
EDV	19 294	10 632	8662
Hospitalization	6 801 810	3 759 760	3 042 050
Death	6 211 580	3 524 505	2 687 075
Vaccine costs	0	376 335	–376 335
Non-medical costs	37 793 483	20 893 808	16 899 675
Working absenteeism	1 198 728	662 559	536 169
Lifetime productivity loss of patient's death	36 594 755	20 231 249	16 363 506
Societal costs[b]	50 873 579	28 591 246	22 282 333
Cost saving/per case averted (healthcare payer perspective)	N/A	2107	N/A
Cost saving/per case averted (societal perspective)	N/A	6338	N/A
Life saved	NA	110	NA

NA, no available; EDV, emergency department visits; HOV, hospital outpatient visits; POV, physician office visits; US$ 1 = NT$ 31.0.
[a]Data are 1-year estimates for a cohort of 34 112 cancer patients in 2002.
[b]Societal costs = medical costs + non-medical costs.

Discussion

Influenza vaccination can have substantial health benefits for persons of any age. Studies have demonstrated that influenza vaccination of persons aged ≥65 years is highly beneficial from an economic standpoint [3,31]. It is less certain whether influenza vaccination of cancer patients aged 20–64 years would result in healthcare system and societal cost savings. A study of working-age cancer patients in the USA found that the effectiveness of the incremental cost-effectiveness ratio of influenza vaccination of working-age cancer patients was 224.00 per quality-adjusted life year gained compared with no vaccination [8]. Our analysis of costs and health outcomes in working-age cancer patients indicates that immunization of adult cancer patients would prevent 42% (2555/6140) of all influenza cases, and would prevent 45% (660/1475) of all serious cases. Thus, in Taiwan, influenza vaccination of cancer patients would provide cost savings of US$5.4 million from the healthcare system perspective and cost savings of US$22.3 million from societal perspective.

This analysis indicates a number of important features in considering the introduction of influenza vaccine for cancer patients. From a healthcare perspective, risk of seeking

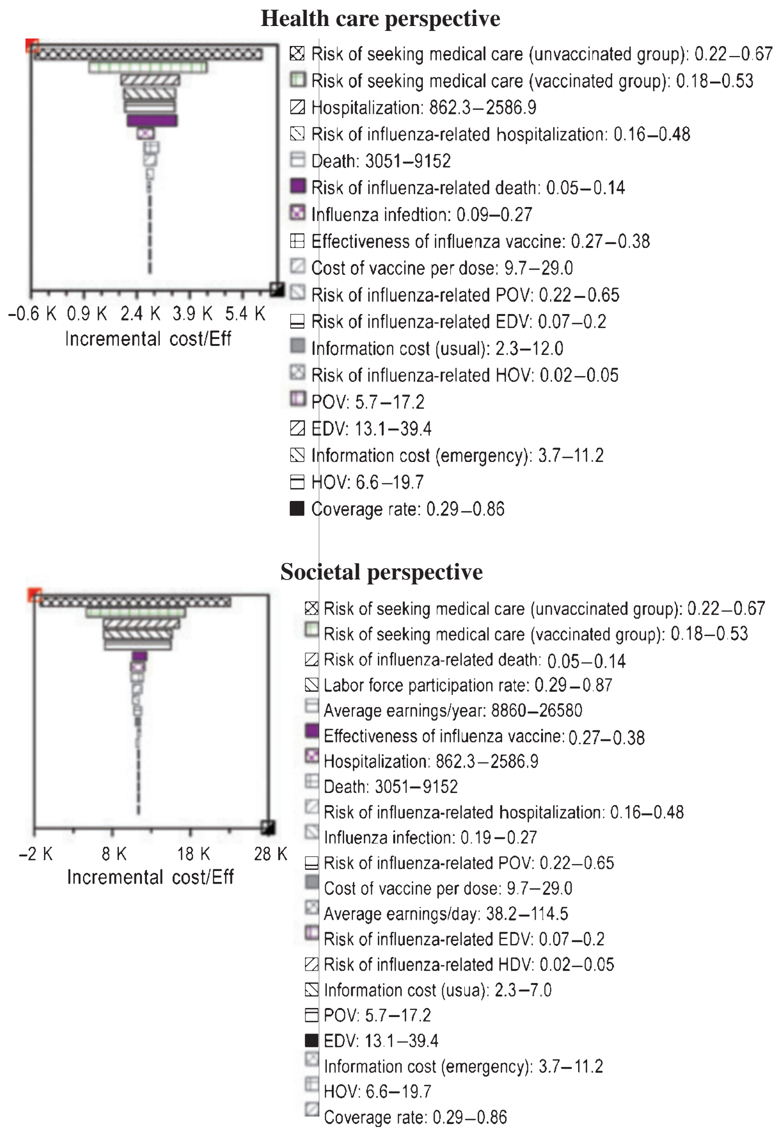

FIG. 2. Tornado chart of univariate sensitivity analyses. Note: each bar represents the range of incremental cost-effectiveness ratios (ICERs) obtained for the ranges of input values shown on the right side. The minimum and maximum input values are shown in the order of ICER values represented by ends of bars. POV, physician office visit; EDV, emergency department visit; HOV, hospital outpatient visit.

medical care for the unvaccinated group, attack rate of influenza, and vaccine coverage were the main determinants of effectiveness. Risk of death due to influenza, labour force participation rate, and average earnings were the important factors for determining societal benefit.

The strength of this study is the utilization of local data on the economic burden of influenza. However, our study has several limitations in the estimation of disease burden and costs. First, we did not use quality-adjusted life-years in our analysis because no data exist on the psychological costs of influenza among cancer patients and their relatives. Future willingness-to-pay studies may better estimate the true value that people attach to the prevention of influenza disease by vaccination. Second, most cases were diagnosed based on clinical pictures, without laboratory evidence from clinical samples, so it is possible that some cases of upper respiratory illness caused by an unknown organism were not related to influenza [32,33]. However, the number of patients with cancer diagnosed with seasonal (autumn and winter) pneumonia and upper respiratory illness caused by an unknown organism was higher than that diagnosed in the spring or summer. It is estimated that the majority of those cases were caused by seasonal influenza infection.

In conclusion, influenza infection is associated with substantial work absenteeism and healthcare resource use among cancer patients aged 20–64 years. This study indicates that administering the influenza vaccine to adult cancer patients is cost-effective in Taiwan from both healthcare and societal perspectives. Annual immunization against influenza for this group is highly recommended.

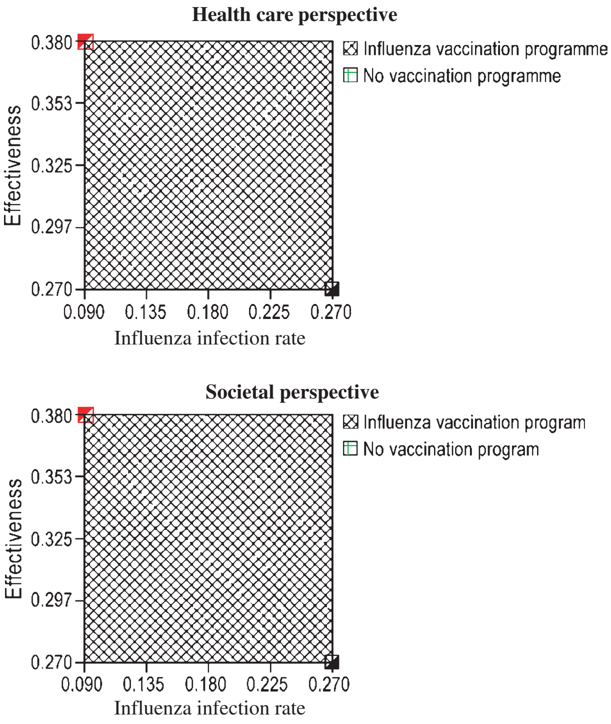

FIG. 3. Cost-effectiveness of the vaccination programme based on probability of influenza infection under a range of estimates of vaccine effectiveness.

Transparency Declaration

This study was supported by the government of Taiwan. The authors report no conflicts of interest.

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