



# Influenza vaccination in acute coronary syndromes patients in Thailand: the cost-effectiveness analysis of the prevention for cardiovascular events and pneumonia

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## Abstract

**Background** Influenza vaccination has been clinically shown to reduce adverse cardiovascular outcomes in acute coronary syndrome (ACS) patients, but the economic perspectives can provide important data to make informed decisions. This study aimed to perform the economic evaluation of lifelong annual influenza vaccination for cardiovascular events and well-established pneumonia prevention. **Methods** Lifetime costs, life-expectancy, and quality-adjusted life years (QALYs) were estimated beyond one-year cycle length of a six-health states Markov model condition on whether a hospitalization for ACS, stroke, heart failure, pneumonia, no hospitalizations occurred, or death. The comparison of three age-groups of 40-year-old-and-above, 50-year-old-and-above, and 65-year-old-and-above scenario was performed. Incremental cost-effectiveness ratio (ICER) and net monetary benefit (NMB) were presented as a societal perspective in 2016. The model robustness was determined by one-way and probabilistic sensitivity analyses. **Results** The influenza vaccination was cost-effective in all age-groups, by dominant ICERs (lower cost with higher effectiveness) which was completely lower than acceptable willingness-to-pay threshold of Thailand [160,000 THB (4,466.8 USD) per QALYs], with a great incremental value of NMB. Especially, the 50-year-old-and-above scenario was shown as the most benefit at 129,092 THB (3,603.9 USD) for each patient. **Conclusions** The annually additional influenza vaccination to standard treatment in ACS was cost-effective in all age-groups, which should be considered in clinical practice and health-policy making process.

*J Geriatr Cardiol* 2018; 15: 413–421. doi:10.11909/j.issn.1671-5411.2018.06.008

**Keywords:** Acute coronary syndrome; Cost-effectiveness; Heart failure; Influenza vaccine; Pneumonia; Stroke

## 1 Introduction

Acute coronary syndromes (ACS) are critical symptoms and major causes of life-threatening disorders in emergency care and hospitalization. Recently, advance recommendation in ACS addresses well-proved drugs and clinical procedures, such as beta-blockers, angiotensin-converting enzyme inhibitors, statins, anti-thrombotics, coronary revascularization, and influenza vaccination.<sup>[1]</sup>

Influenza vaccination is well-established to reduce hospitalization and mortality due to pneumonia or influenza,<sup>[2–4]</sup> cardiovascular disease,<sup>[2–4]</sup> chronic heart failure (HF)<sup>[5]</sup> and cerebrovascular disease.<sup>[4]</sup> Randomized controlled trial also shows benefit of major adverse cardiovascular event prevention in ACS patients.<sup>[6]</sup> In addition, influenza vaccination is recommended as a secondary prevention in coronary artery disease, atherosclerotic vascular disease,<sup>[7]</sup> and ACS.<sup>[1]</sup>

Influenza vaccination has been shown to reduce adverse cardiovascular outcomes and recommended in ACS patients, but the information of added benefit for cardiovascular event and pneumonia prevention does not exist.

Not only are the evidences of clinical benefits essential for considerations, the economic perspectives for clinicians and policy-makers are also strongly important. Especially, the economic evaluation of lifelong annual influenza vacci-

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**Received:** December 13, 2017

**Revised:** February 7, 2018

**Accepted:** March 20, 2018

**Published online:** June 28, 2018

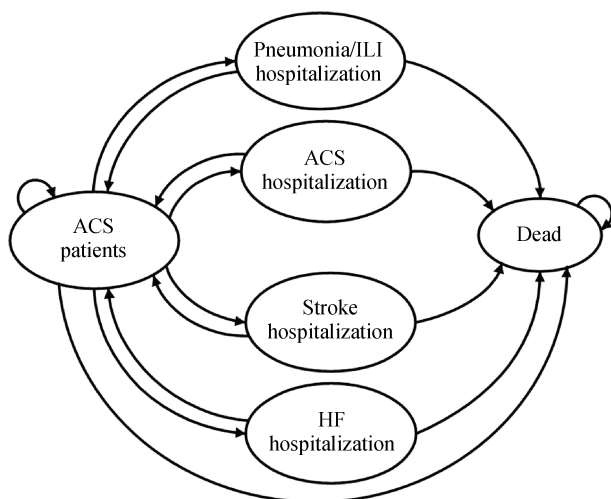
nation for the prevention of cardiovascular events and well-established pneumonia has never been reported.

Therefore, this study aimed to perform the economic evaluation of lifelong annual influenza vaccination for cardiovascular event prevention and well-established pneumonia prevention in ACS patients.

## 2 Methods

### 2.1 Economic model

A six-health-states Markov model was performed to evaluate outcomes and cost of each scenario in ACS patients with one-year of cycle-length (Figure 1). All health-states were formed of (1) ACS patients without any interested events, (2) ACS patients who were possibly hospitalized due to influenza or pneumonia, or (3) recurrent event of ACS, (4) stroke, (5) HF, or (6) death. The lifetime horizon view was simulated to determine long-term cost and total effectiveness. Therefore, the model analysis was run until patients aged 100 years old, or no more patients remained in model cohort. The perspectives of analyses were shown as societal view.



**Figure 1.** The Markov model structure of ACS patients comprises six health-states. ACS: acute coronary syndrome; HF: heart failure.

### 2.2 Interventions and comparators

A trivalent, inactivated influenza vaccine (Vaxigrip<sup>®</sup>, Sanofi Pasteur) was intramuscularly given annually with standard treatment for ACS patients compared with those received standard treatment without vaccination. The vaccination was assumed as lifelong annual administration. However, the cumulative effectiveness of vaccination was

assumed that there was no remaining treatment effect in subsequent years when patients received two and more consecutive years of vaccination.

The proportion of ACS age groups in Thailand, described as 40–49 years, 50–65 years and > 65 years, was presented in 13.8%, 32.0%, 54.2%, respectively.<sup>[8,9]</sup> The 40 years old and above was the major group approximately covered 97.0% of total of ACS patients.<sup>[8]</sup> For this reason, the comparison of three age-groups of 40-year-old-and-above, 50-year-old-and-above, and 65-year-old-and-above was assigned. Nevertheless, the complete vaccination coverage for all age-group scenarios was assumed.

These age-groups as non-discrete gender classification, were estimated to represent the proportion of total acute coronary syndrome patients who would be enrolled in each strategic scenario. However, the other age-group classifications from the registry in Thailand revealed that male patients proportions were dominantly performed in all age-groups (< 45 years, 85%; 45–54 years, 75%; > 54 years, 54%).<sup>[8]</sup>

### 2.3 Input parameters

#### 2.3.1 Likelihood of events

The majority of transition-probabilities were derived from Phrommintikul, *et al.*,<sup>[6]</sup> but the others were derived from sources of Thailand and other countries in order to project the prevention for cardiovascular events and pneumonia.

All transition-probabilities of patients' age in simulated cohorts were generally performed at 50 years old and above (Table 1), but stroke health-state applied at 45 years old and above,<sup>[4,9–13]</sup> while pneumonia or influenza-like-illness (ILI) started at 65 years old.<sup>[2–4,14,15]</sup>

Likewise, the vaccine effectiveness normally began at 50 years,<sup>[6]</sup> but the benefit for pneumonia/ILI<sup>[2]</sup> and stroke hospitalization<sup>[4]</sup> were performed at 65 year old and above. These following transition-probabilities assumption of (1) pneumonia/ILI hospitalization,<sup>[3,4,14,15]</sup> (2) vaccine effectiveness for pneumonia/ILI,<sup>[2]</sup> (3) death after pneumonia hospitalization,<sup>[2]</sup> (4) vaccine effectiveness for death after pneumonia hospitalization,<sup>[2]</sup> (5) vaccine effectiveness for stroke prevention,<sup>[4]</sup> were assigned as the same as those revealed in the population of elders living in long-term care facilities.

In addition, the vaccine effectiveness for death after HF in ACS was assumed to be similar to those effectiveness with chronic HF.<sup>[5]</sup> The transition-probability of death for ACS patients who had no event, was based on age-specific

**Table 1. Input parameters.**

Parameters	Base case	Lower range	Upper range	Source
Transition probabilities				
Pneumonia/ILI hospitalization	0.0102	0.0044	0.0235	[3,4,14,15]
ACS hospitalization	0.1125	0.0729	0.1640	[6]*
Stroke hospitalization	0.0106	0.0067	0.0150	[9–13]
HF hospitalization	0.0479	0.0233	0.0863	[6]*
Death after pneumonia/ILI hospitalization	0.0426	0.0000	0.1579	[2]
Death after ACS hospitalization	0.0862	0.0108	0.2780	[6]*
Death after stroke hospitalization	0.5200	0.4420	0.5980	[32]
Death after HF hospitalization	0.2077	0.0278	0.5688	[6]*
Effectiveness of influenza vaccine				
Pneumonia/ILI hospitalization	0.4220	0.4012	0.4413	[2]
Death after pneumonia/ILI hospitalization	0.4600	0.3300	0.6300	[2]
ACS hospitalization	0.4430	0.2153	0.9115	[6]*
Stroke hospitalization	0.4350	0.3976	0.4709	[4]
HF hospitalization	0.2250	0.0624	0.8117	[6]*
Death after HF hospitalization	0.8100	0.6700	0.9700	[5]
Utilities				
No event ACS	0.8420	0.6320	1.0000	[22]
Pneumonia/ILI hospitalization	0.4000	0.3800	0.5000	[23]
ACS hospitalization	0.7790	0.5840	0.9740	[22]
Stroke hospitalization	0.6900	0.6000	0.7800	[24,25]
HF hospitalization	0.7590	0.6806	0.8374	[26]
Cost (THB, at 2016)				
Direct medical cost				
No event ACS	64,133.72	54,513.67	73,753.78	[17]
Pneumonia/ILI hospitalization	33,019.76	1,335.10	1,517,155.95	Hospital database
ACS hospitalization	189,841.18	161,365.01	218,317.36	[17]
Stroke hospitalization	66,943.86	56,902.28	76,985.44	[18]
HF hospitalization	334,961.22	327,394.30	341,991.64	[19]
Influenza vaccine	289.80	189.61	403.62	[33]
Direct non-medical cost				
No event ACS	3,651.45	3,103.73	4,199.16	[17] <sup>#</sup>
Pneumonia/ILI hospitalization	660.03	561.03	759.04	[20]
ACS hospitalization	3,651.45	3,103.73	4,199.16	[17]
Stroke hospitalization	69,308.76	58,912.44	79,705.07	[18]
HF hospitalization	3,651.45	3,103.73	4,199.16	[17] <sup>#</sup>

\*Data were re-analysed from original data of Phrommintikul, *et al.*<sup>[6]</sup> which adjusted by patients' age; <sup>#</sup>data were assumed as same as direct non-medical cost of ACS hospitalization. ACS: acute coronary syndrome; HF: heart failure; ILI: influenza-like illness; THB: Thai baht.

mortality rate for Thai population by World Health Organization (WHO).<sup>[16]</sup>

All original data as risk or proportion within exact periods of follow-up time, or event rate were converted to one-year transition-probabilities. In each cohort simulation, the multiplication of proportions of ACS population for each age group<sup>[8]</sup> were used to determine the transition-probabilities. As well as influenza vaccination cohort simu-

lation, vaccine effectiveness was also multiplied by other transition-probabilities.

### 2.3.2 Costs

The direct medical cost (DMC) assumption of each health-state in ACSs defined as (1) pneumonia/ILI, where the OPD visit follow-up after hospitalization was not included, while (2) hospitalized due to ACS,<sup>[17]</sup> (3) stroke,<sup>[18]</sup>

or (4) HF<sup>[19]</sup> was described as a total cost. In case of (5) no event ACS health state, the total cost determination was indicated as a difference between the first year cost and the first hospitalization cost.<sup>[17]</sup>

The DMC of pneumonia/ILI was obtained from hospital database by patients' identification of ICD-10 code (J9-J18) as influenza and pneumonia, then converted by cost-to-charge ratio method. The direct non-medical cost (DNMC) for each health-state of hospitalization due to HF, ACS and no event ACS<sup>[17]</sup> was assumed to be similar between groups, where DNMC of pneumonia/ILI was estimated via standard cost list<sup>[20]</sup> consisting fare cost, additional food cost and loss of income for both patients and caregivers.

All costs were adjusted by consumer price index of Thailand<sup>[21]</sup> to present value of the year 2016, where annual discount rates for cost and clinical benefits were assigned at 3%. The money values of costs in Thai baht (THB) can be converted into US dollar (USD) by an average exchange rate of 35.82 THB per USD at the end of 2016.

However, a total cost determination was not included an indirect cost or productivity loss to avoid a repeated counting procedure because the utilities had been adjusted as quality-adjusted life years (QALYs), which the morbidity and mortality effect were counted.

### 2.3.3 Utilities

The utilities for each health state<sup>[22-26]</sup> were used to adjust life years gained in patients of vaccination and non-vaccinated group, where performed as QALYs.

## 2.4 Data analysis

### 2.4.1 Base-case analysis

The deterministic results were calculated via base-case values of model (Table 1), where presented as life years, QALYs, total cost, incremental cost-effectiveness ratios (ICERs) and net monetary benefits (NMBs). All outcome results were demonstrated in three age groups of 40-year-old-and-above, 50-year-old-and-above and 65-year-old-and-above.

### 2.4.2 Sensitivity analysis

The uncertainty was determined by one-way sensitivity analysis and probabilistic sensitivity analysis (PSA).

All feasible ranges of each parameter were input to address an uncertainty of ICERs as extremely situation (Table 1); these results were demonstrated as a tornado diagram.

The PSA distribution types of input parameters were properly assigned to demonstrate the feasible value. The margin of data ranges was assumed at 15%, where specific ranges or confidence intervals were not available.

The Monte Carlo simulation was performed to randomly

draw from all feasible ranges, and then computed the expected cost and outcomes of each strategy. A fifteen-thousand iterations of analysis were assigned, and the scatter plots of ICERs were displayed to describe robustness of scenarios.

The cost-effectiveness acceptability curve (CEAC) displayed to explain the relationship between the probability that strategy was favouring cost-effectiveness, and the proper ceiling threshold of willingness-to-pay (WTP) per QALYs to conduct an evidence-based decision making.

The cost-effective decision making was based on WHO recommendation, an intervention that costed less than three times the national annual per capita gross domestic product (GDP) was considered cost-effective, where highly cost-effective intervention was indicated when the national annual GDP less than once.

### 2.4.3 Ethical approval

This study was approved by the Ethics Committees, Faculty of Medicine, Chiang Mai University.

## 3 Results

### 3.1 Base-case analysis

The 40-year-old-and-above scenario with standard treatment and added influenza vaccination revealed 19.64 and 20.35 life years gained, respectively (Table 2). Thus, influenza vaccination increased 0.71 live years per patients, and 0.27 QALYs (Table 2). While, the 50-year-old-and-above, and 65-year-old-and-above group showed 0.88 and 0.49 live years gained, with higher QALYs by 0.44 and 0.31, respectively; where the 50-year-old-and-above strategy demonstrated the highest gain.

The lifetime cost of an added influenza vaccination of the 40-year-old-and-above scenario was highest price at 1,048,639 THB (29,275.2 USD), while the 50-year-old-and-above and 65-year-old-and-above scenario revealed 794,495 THB (22,180.2 USD), and 462,875 THB (12,922.3 USD), respectively. However, the lifetime cost of annual influenza vaccination was lower than standard treatment in all age-group strategies.

The annually added influenza vaccination to standard treatment performed substantially cost-effective in all strategic treatments, where by dominant ICERs (lower cost with incremental effectiveness) was demonstrated completely lower than acceptable WTP of Thailand at 160,000 THB (4,466.8 USD) per QALYs gained.

Additionally, an incremental value of NMB for all three scenarios revealed a great benefit. Especially, the 50-year-old-and-above scenario was shown as the most value at

**Table 2. The base-case outcomes analyses of a three-strategies of 40 years old and above, 50 years old and above and 65 years old and above scenarios.**

Scenarios	Standard Care	Influenza vaccination	Incremental value	ICER
40-year-old-and-above				
Cost, THB	1,083,874	1,048,639	-35,235	-
LYs gained, yrs	19.64	20.35	0.71	Dominant (THB/LYs gained)
QALYs gained, yrs	12.08	12.34	0.27	Dominant (THB/QALYs gained)
NMB, THB	848,520	926,278	77,758	-
50-year-old-and-above				
Cost, THB	852,992	794,495	-58,497	-
LYs gained, yrs	12.89	13.77	0.88	Dominant (THB/LYs gained)
QALYs gained, yrs	8.71	9.15	0.44	Dominant (THB/QALYs gained)
NMB, THB	540,067	669,159	129,092	-
65-year-old-and-above				
Cost, THB	521,295	462,875	-58,420	-
LYs, yrs	6.49	6.98	0.49	Dominant (THB/LYs gained)
QALYs gained, yrs	4.85	5.16	0.31	Dominant (THB/QALYs gained)
NMB, THB	254,673	363,195	108,523	-

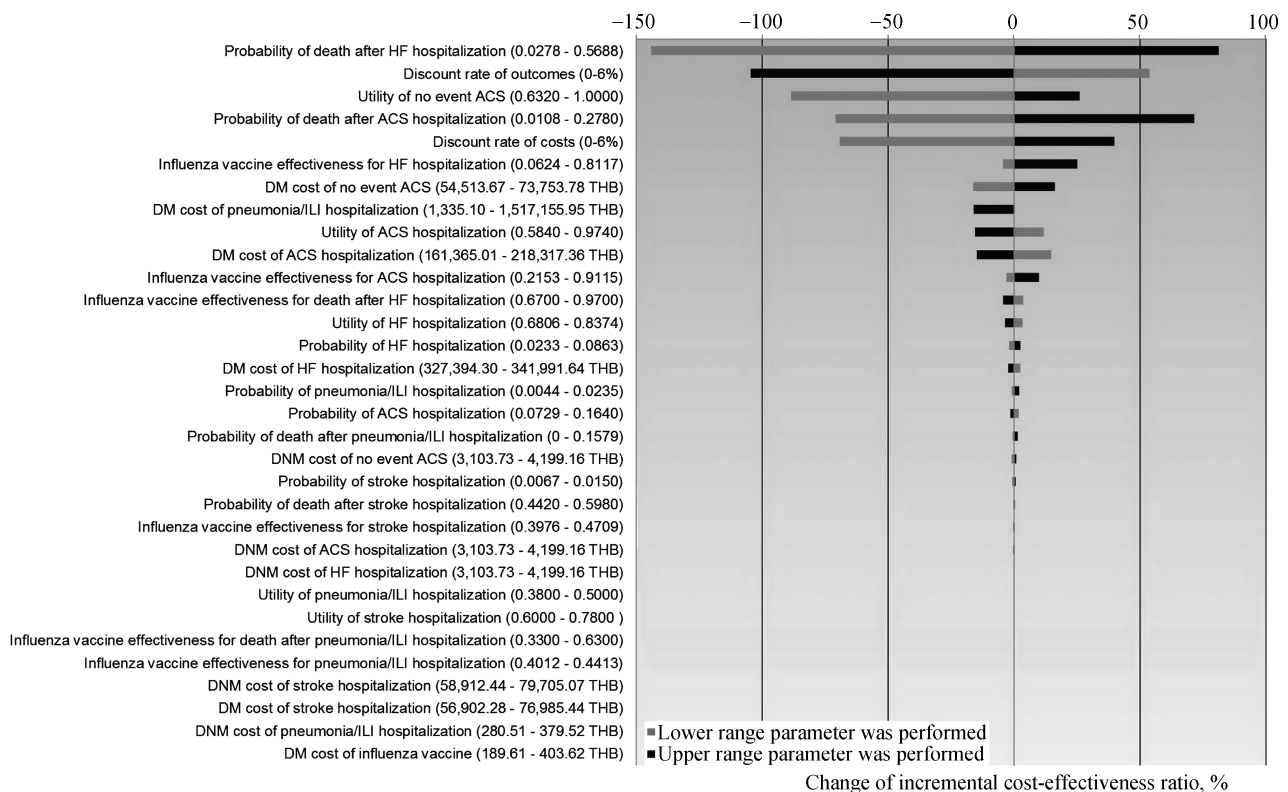
ICER: incremental cost-effectiveness ratio; LYs: life-years; NMB: net monetary benefit; QALYs, quality-adjusted life years; THB: Thai Baht.

129,092 THB (3,603.9 USD) over the others, when the most gain of QALYs had been considered.

**3.2 Sensitivity analysis**

The tornado diagram showed that the probability of death

after HF hospitalization was the most influential variable. The probability varied from 0.0278 to 0.5688 (Table 1) to generate the ICERs of added influenza vaccination compared with standard treatment was shifted from -144.13% to 81.27% (Figure 2).



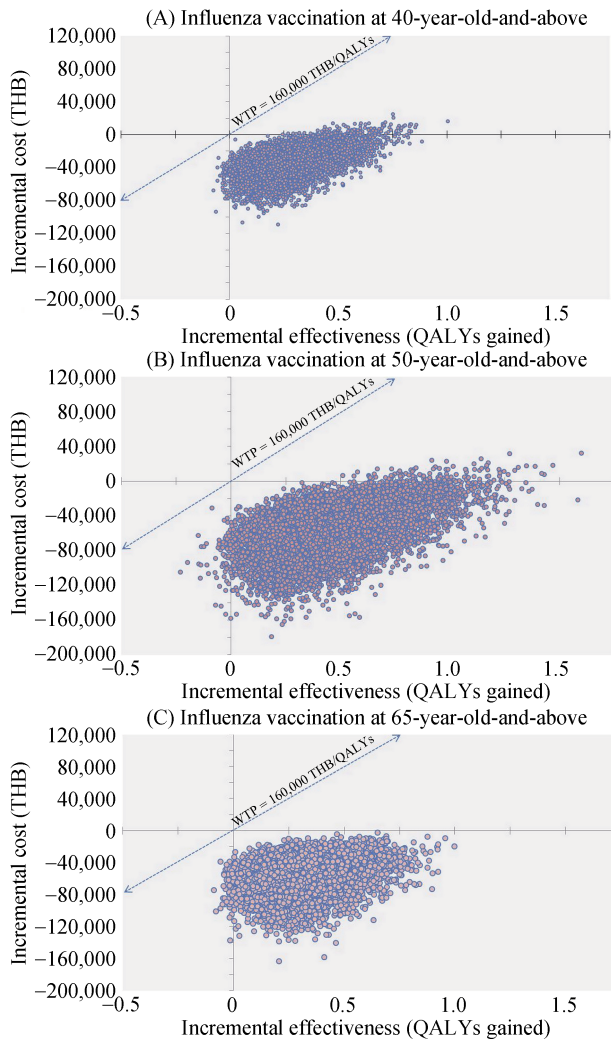
**Figure 2. Tornado diagram revealed two-way sensitivity analyses between standard treatment and influenza vaccination.** These data were based on patients who were 40 years old and above, while percentage of relative change in incremental cost-effectiveness ratios of all variables were based on -132,578.38 THB/QALYs. ACS: acute coronary syndrome; DM cost: direct medical cost; DNM: direct non-medical cost; HF: heart failure; ILI: influenza-like illness.

In addition, the cost-effectiveness plans of PSA, at a WTP-threshold of Thailand revealed that all scenarios were very cost-effective (Figure 3).

Moreover, all of CEAC indicated that added influenza vaccination was completely cost-effective compared with a standard treatment (Figure 4).

## 4 Discussion

This cost-effectiveness study in ACS patients showed that the influenza vaccination was cost-effective to prevent



**Figure 3.** The scatter plots of cost-effectiveness planes were conducted to compare the incremental outcomes (cost and QALYs) of influenza vaccination to standard treatment for each scenario. (A): 40-year-old-and-above, (B): 50-year-old-and-above, and (C) 65-year-old-and-above. These probabilistic sensitivity analysis were performed by a total of 15,000 iterations of Monte Carlo simulation, which all revealed lower than the willingness-to-pay threshold of Thailand (160,000 THB/QALYs). QALYs: quality-adjusted life years; THB: Thai Baht.

cardiovascular events and pneumonia. Especially, the prevention of cardiovascular event has never been included in any previous health-economic evaluation of influenza vaccination.

All results disclosed that the annually added influenza vaccination to standard treatment in ACS patients was substantially cost-effective in all three-strategic treatments of age-groups, by dominant ICERs that were all completely lower than acceptable WTP of Thailand. An incremental value of NMB for all three scenarios also revealed a great benefit, especially the 50-year-old-and-above group was shown as the most benefit scenario at 129,092 THB (3,603.9 USD) over the others.

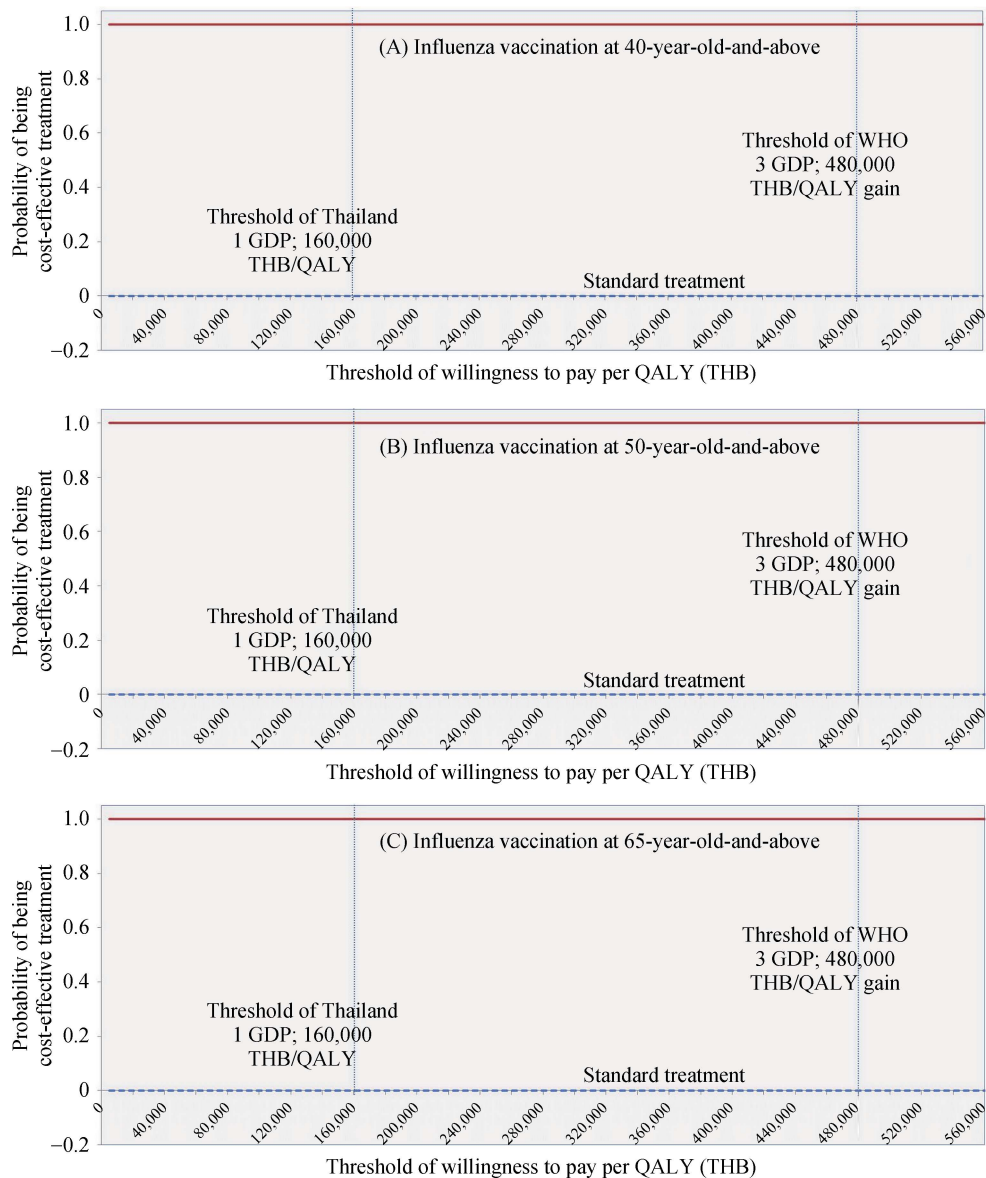
The most probabilities of events in Markov model normally started at 50 years old, and vaccine effectiveness was also presented at 50 years and 65 years old. Moreover, the proportion of ACS patients of the 50-year-old-and-above group was greater than 80% of ACS populations.<sup>[8]</sup> For this reason, the budget forecasting for the 40-year-old-and-above scenario would not show any lower incremental budgets before the first 10-years of implementation.

Although the result showed the lowest NMB of the 40-year-old-and-above scenario, the scenario was not the first-choice strategic treatment for health policy decision making, but the established advantage of influenza vaccination in age range of 40–59 years old was also demonstrated, such as the prevention of proven influenza infection, ILI, illness days, working day lost or physicians visits in healthy adults.<sup>[27]</sup>

The benefit of influenza vaccination for different target population groups without any exception of age groups was also recommended in clinical guidelines<sup>[1,7,28]</sup> and established as a widely national policy,<sup>[29]</sup> such as in occupational settings and clinical risk groups.<sup>[29]</sup>

As mentioned above, the influenza vaccination was strongly recommended for people who met all of proper indications for benefits, even in age lower than 50 years old. In addition, the proportion of ACS of the 40-year-old-and-above group was approximately more than 95% of a total of ACS patients in Thailand,<sup>[8]</sup> where represented a total cost and benefits of total ACS patients. These approximations could reflect the possible health-perspectives to policy maker considerations, if the vaccination scenario for all ACS patients is feasible to implement.

Certainly, the strategy of influenza vaccination for 40 years old patient and above should be strongly recommended. Despite the first 10-years implementation would not show some budget reduction, the life-long cost saving was strongly revealed.



**Figure 4.** These cost-effectiveness acceptability curves demonstrated the cost-effective probability of three scenarios of patients' age. (A): 40-year-old-and-above, (B): 50-year-old-and-above, and (C) 65-year-old-and-above, by each threshold of willingness-to-pay in ACS patients who had a standard treatment or added influenza vaccination. ACS: acute coronary syndrome; QALYs: quality-adjusted life years; THB: Thai Baht.

However, this economic model construction of influenza vaccination did not consume the benefit of indirect protection, such as the vaccination of health-care workers showed reductions in mortality among the elders in long-term care setting. Although, the history of a few previous consecutive annual vaccinations showed benefit for major adverse vascular event prevention,<sup>[30]</sup> they were not included in the construction of this study model.

Moreover, some evidences showed that incomplete match influenza vaccine still provided protection in frail elders<sup>[31]</sup> or high-risk medical conditions.<sup>[30]</sup> The model de-

terminatively incorporated all evidences with and without influenza matching to reflect as much as possible benefit perspectives of influenza vaccination.

In conclusion, this study showed that standard care with lifetime annual influenza vaccination in ACS patients was potentially cost-effective in prevention of cardiovascular events and pneumonia compared with those without added vaccination. All scenarios revealed completely cost-effective scenarios, especially the two-great-NMB of 50-year-old-and-above, and 65-year-old-and-above group.

These evidence-based benefits should be noteworthy

considered in routine clinical practice and decision-making process for health-policy makers, especially under the limited healthcare resources in recent global economic situation.

## Acknowledgement

We declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. We thank Dr. Surasak Saokaew (University of Phayao, Thailand) and Onwipa Rochanathimoke (PhD student of Mahidol University, Thailand for technical analysis advice. Phrommintikul A was supported by Thailand Research Fund (RSA5780040). Wongcharoen W was supported by Thailand Research Fund (RSA5780039).

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