COST-UTILITY EVALUATION OF INFLUENZA VACCINATION IN PATIENTS WITH EXISTING CARDIOVASCULAR DISEASES IN THAILAND

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A Dissertation Submitted in Partial Fulfillment of the Requirements
for the Degree of Doctor of Philosophy Program in Social and Administrative Pharmacy
Department of Social and Administrative Pharmacy
Faculty of Pharmaceutical Sciences
Chulalongkorn University
Academic year 2011

การวิเคราะห์ต้นทุนอรรถประโยชน์ของการให้วัคซีนป้องกันไข้หวัดใหญ่ในผู้ป่วยโรคหัวใจและหลอดเลือดในประเทศไทย

นางพงศ์พญา ชูสกุลชาติ

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรดุษฎีบัณฑิต
สาขาวิชาเภสัชศาสตร์สังคมและบริหาร ภาควิชาเภสัชศาสตร์สังคมและบริหาร
คณะเภสัชศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย
ปีการศึกษา 2554

พงศ์พญา ชูสกุลชาติ : การวิเคราะห์ต้นทุนอรรถประโยชน์ของการให้วัคซีนป้องกันไข้หวัดใหญ่ในผู้ป่วยโรคหัวใจและหลอดเลือดในประเทศไทย (COST-UTILITY EVALUATION OF INFLUENZA VACCINATION IN PATIENTS WITH EXISTING CARDIOVASCULAR DISEASES IN THAILAND)

อ. ที่ปรึกษาวิทยานิพนธ์หลัก : ผศ.ภญ. ร.ต.อ.หญิง ดร. ฐณัฏฐา กิตติโสภี, 130 หน้า.

ไข้หวัดใหญ่สามารถทำให้อาการโรคหัวใจเรื้อรังทรุดหนักขึ้นและนโยบายสุขภาพแนะนำให้ฉีดวัคซีนไข้หวัดใหญ่ในกลุ่มผู้ป่วยกลุ่มนี้ อย่างไรก็ตามต้นทุนประสิทธิผลของการฉีดวัคซีนไข้หวัดใหญ่ในการปกป้องผู้ป่วยโรคหลอดเลือดหัวใจยังไม่ได้มีศึกษาอย่างชัดเจนโดยเฉพาะอย่างยิ่งในความรุนแรงของโรคที่แตกต่างกัน แบบจำลองมาร์คอฟแสดงการดำเนินไปของโรคหลอดเลือดหัวใจร่วมกับการติดเชื้อไข้หวัดใหญ่ได้รับการพัฒนาขึ้นเพื่อประมาณค่าใช้จ่ายตลอดชีวิตและผลกระทบต่อสุขภาพของการฉีดวัคซีนไข้หวัดใหญ่เมื่อเทียบกับการไม่ฉีดวัคซีนในกลุ่มผู้ป่วยต่อไปนี้: 1) ผู้ป่วยที่มีประวัติแน่นหน้าอกเรื้อรัง; 2) ฉีดวัคซีนไข้หวัดใหญ่ในผู้ป่วยที่มีประวัติกล้ามเนื้อหัวใจตายหรือหัวใจหยุดเต้น; และ 3) ฉีดวัคซีนไข้หวัดใหญ่ในผู้ป่วยโรคหลอดเลือดหัวใจทั้งหมด การวิเคราะห์ต้นทุนประสิทธิผลเปรียบเทียบระหว่างการฉีดวัคซีนทุกทางเลือกเพื่อประเมินประสิทธิผลสูงสุดจากมุมมองทางสังคม และผลกระทบต่อสุขภาพโดยใช้โปรแกรมสำเร็จรูป (TreeAge) การวิเคราะห์ความไวของผลลัพธ์ที่เกิดจากความไม่แน่นอนของตัวแปรในแบบจำลองแบบไม่อาศัยความน่าจะเป็นและแบบอาศัยความน่าจะเป็น เพื่อระบุตัวแปรที่มีอิทธิผลต่อผลลัพธ์และความมั่นคงของผลการวิเคราะห์ ผลการศึกษาแสดงอัตราส่วนต้นทุนประสิทธิผลที่เพิ่มขึ้น (ICER) ดังนี้ ในผู้ป่วยที่มีประวัติแน่นหน้าอกเรื้อรัง เท่ากับ 8,420, ในผู้ป่วยที่มีประวัติกล้ามเนื้อหัวใจตายหรือหัวใจหยุดเต้น เท่ากับ 62,711, และ ผู้ป่วยโรคหลอดเลือดหัวใจทั้งหมด เท่ากับ 33,813 บาท ต่อปีชีวิตที่มีคุณภาพเพิ่มขึ้น โดย ทางเลือกที่มีความคุ้มค่าทางเศรษฐศาสตร์สูงสุดคือ การให้วัคซีนไข้หวัดใหญ่ในผู้ป่วยที่มีประวัติแน่นหน้าอก เมื่อพิจารณาความเต็มใจที่จะจ่าย (WTP) ตามเกณฑ์ที่กำหนดโดยคณะกรรมการบัญชียาหลักแห่งชาติปี 2554 ที่ 100,000 บาท ต่อ ปีชีวิตที่มีคุณภาพ การให้วัคซีนในกลุ่มผู้ป่วยโรคหลอดเลือดหัวใจทั้งหมด ให้ จำนวนปีชีวิตที่มีคุณภาพสูงกว่าทางเลือกอื่น โดยที่อัตราส่วนต้นทุนประสิทธิผลที่เพิ่มขึ้นยังคงน้อยกว่า WTP ตามเกณฑ์ที่กำหนด ดังนั้นการฉีดวัคซีนในกลุ่มนี้จึงมีความเหมาะสมและควรถูกแนะนำ

ผลการศึกษาสอดคล้องกับข้อแนะนำการให้วัคซีนไข้หวัดใหญ่ทั้งในสากลและประเทศไทย มีรายงานการใช้วัคซีนไข้หวัดใหญ่น้อยกว่าที่ควร ดังนั้นการใช้วัคซีนไข้หวัดใหญ่ควรได้รับการส่งเสริมอย่างจริงจัง

ภาควิชา : เภสัชศาสตร์สังคมและบริหาร ลายมือชื่อนิสิต.....

สาขาวิชา: เภสัชศาสตร์สังคมและบริหาร ลายมือชื่อ อ.ที่ปรึกษาวิทยานิพนธ์หลัก.....

ปีการศึกษา 2554

5177112933 : MAJOR SOCIAL AND ADMINISTRATIVE PHARMACY
KEYWORDS : COST / UTILITY / INFLUENZA VACCINE / CORONARY HEART / THAILAND

PONGPHAYA CHOOSAKULCHART : COST-UTILITY EVALUATION OF INFLUENZA VACCINATION IN PATIENTS WITH EXISTING CARDIOVASCULAR DISEASES IN THAILAND. ADVISOR : ASST. PROF. TANATTHA KITTISOPEE, Ph.D, 130 pp.

Influenza can exacerbate chronic coronary heart disease (CHD) and health policy recommends influenza vaccination in this patient group. However, the cost effectiveness of influenza vaccination in protecting CHD patients has not been well studied before especially in different disease severities. The Markov model of CHD progression concurrent with influenza infection was developed to quantify the life-time costs and health effects of the three influenza vaccination strategies in: 1) Angina patients; 2) Cardiac Arrest/Myocardial Infarction (CA/MI) patients; 3) CHD combined group, versus no influenza vaccination. Cost-effectiveness analysis (CEA) comparing between the three vaccination strategies was performed to assess the highest effectiveness from a societal perspective. Decision analysis software (TreeAge) was used to explore relative cost-effectiveness of influenza vaccination strategies. Deterministic and probabilistic analyses were performed to identify variables that influence the sensitivity of the result and the robustness of the study model. The results showed Incremental Cost Effectiveness (ICER) of vaccination in Angina patient, in CA/MI patients, and in CHD combined group as 8,420, 62,711 and 33,813 THB per QALY gained, respectively; therefore, the highest cost-effectiveness is vaccination in Angina patients. Considering willingness to pay (WTP) threshold at 100,000 THB per QALY as accepted by Thai National Formulary 2010, influenza vaccination in CHD combined group is the most optimal and should be recommended as it yielded highest QALYs gained while it is still within WTP threshold.

The study results are in accordance with the current influenza vaccine recommendation, both international and Thailand. Influenza vaccine underutilization has been reported; therefore, strongly promoting the administration of influenza vaccination to CHD patients is highly recommended.

Department : Social and Administrative Pharmacy Student's Signature .....

Field of Study : Social and Administrative Pharmacy Advisor's Signature .....

Academic Year : 2011 .....

ACKNOWLEDGEMENTS

I would like to express my gratitude to Assistant Prof. Tanattha Kittisopee, Ph.D. my advisor, for valuable advices, guidance, consulting, coaching, support and, encouragement during this study truly help the progression and success of my dissertation.

The special appreciation goes to Suchet Takdhada, M.D. for his inputs on the research design as well as his suggestion and comments on data inputs though the whole modeling process.

I wish to express my appreciation to Yoel Lubell, Ph.D. who provide precious suggestions and comments to the economic mode as well as the data analysis.

The special thank you goes to Mrs. Janet Robinson who provided review to my publication as well as provided helpful support to the analysis as well as Mr. Thanawi phatiphacharawong and all the staff at Department of Social and Administrative Pharmacy who provided continuously help in administrative work though out my study.

The great deals appreciated goes to the contribution of my faculty – Faculty of Pharmaceutical Sciences. I am also would like to thankful all instructors at Department of Social and Administrative Pharmacy and all of my classmates who provided feedbacks and opinions to my dissertation during the class seminars.

Finally, my deep gratefulness goes to my family members for their continuous encouragement, understanding, as well as being my inspiration for the success in my Ph.D. degree.

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LIST OF ABBREVIATIONS

ACC	American College of Cardiology
ACIP	Advisory Committee on Immunization Practices
ACS	Acute Coronary Syndrome
AHA	The American Heart Association
AMI	Acute Myocardial Infarction
CABG	Coronary Artery Bypass Grafting
CAD	Coronary Artery Disease
CA/MI	Cardiac Arrest/Myocardial Infarction
CBA	Cost-Benefit Analysis
CCS	Canadian Cardiovascular Society
CEA	Cost-Effectiveness Analysis
CHD	Coronary Heart Disease
CHF	Congestive Heart Failure
CMA	Cost-Minimization Analysis
CPI	Consumer Price Index
CUA	Cost-Utility Analysis
CVA	Cerebrovascular Accident
CVD	Cerebrovascular Disease

LIST OF ABBREVIATIONS (CONT.)

DE	Demographic-Epidemiologic
DH	Disease History
DSA	Deterministic Sensitivity Analysis
EQ-5D	EuroQoL
GBS	Guillian-Barré Syndrome
HA	Glycoproteins Hemagglutinin
HISO	Health Information System Development Office
HR	Hazard ratio
HRQOL	Health-Related Quality of Life
HUI	Health Utilities Index
ICER	Incremental Cost-Effectiveness Ratio
IHD	Ischemic Heart Disease
ILI	Influenza-Like-Illness
IM	Intramuscular Injection
IPD	In patient Department
LAIV	Live Attenuated Influenza Vaccine
LYG	Lift Year Gained
MACE	Major Adverse Cardiac Events
MOPH	Ministry of Public Health

LIST OF ABBREVIATIONS (CONT.)

NA Neuraminidase

NHSO National Health Security Office

OPD Outpatient Department

PCA Primary Cardiac Arrest

PCI Percutaneous Coronary Intervention

PE Pharmcoeconomic Evaluation

PROBE Prospective Randomized Open with Blinded Endpoint

PSA Probabilistic Sensitivity Analysis

QALY Quality Adjusted Life Years

QWB Quality of Well-Being

RCT Randomized Controlled Trial

RR Risk Ratio/Relative Risk

RS Rating Scale

SE Standard Error

SF-36 Short-form 36 Questionnaire

SG Standard Gamble

SF-6D Short Form Six-Dimension

TTO Time Trade-Off

VAS Visual Analogue Scale

LIST OF ABBREVIATIONS (CONT.)

VE	Vaccine Effectiveness
WTP	Willingness to Pay

CHAPTER I

INTRODUCTION

1. Background and Significance of the problem

The leading chronic illness among Thai's is cardiovascular disease. Twenty eight percent of Thais have some form of cardiovascular disease; heart attack and stroke kill 65,000 Thai's per year.[1] Individuals with chronic coronary heart diseases (CHD) may have increased risks for complications from influenza infection leading to severe illness or death. Recently, there are reports detecting an increasing patient numbers with acute coronary syndromes (ACS) during influenza season.[2,3] More recently, there are case-controlled studies of prior infarction patients which have shown the significant reduction in the risk of myocardial necrosis and strokes from influenza vaccination.[4] This evidence has led to the recommendation that influenza immunization be given to people with coronary and other atherosclerosis.[5]

While the health impact and treatment/intervention expenditures for CHD at different severities are different, the annual influenza vaccine recommendation for CHD patients is not severity specific. The Advisory Committee on Immunization Practices (ACIP) recommends influenza vaccination[6] to elderly individuals and chronically ill patients of any age with medical conditions which generally include patients with CHD of all severity. The American Heart Association (AHA) and American College of Cardiology (ACC) are more specific in their influenza immunization recommendation as a part of comprehensive secondary prevention in coronary and other atherosclerosis patients (Class I Level B) but the recommendation does not particularly include disease severity in the consideration.[7] Moreover CHD patients who have similar functional limitation differ substantially in their symptoms tolerance, as measured by utility; therefore, it is suggested that guidelines for the ischemic heart diseases management should also include patient's preference rather than symptom severity alone.[8]

For Thailand, the National Health Security Office (NHSO) provides influenza vaccination to patients with high risk medical condition that includes heart disease but the disease severity is also not included in the provision consideration.[9]

Resources are always limited and the number of patients with CHD is increasing each year and CHD is now considered as one of the chronic diseases requiring long-term healthcare. In addition seasonal strains vary and each annual vaccine production includes the strains most predicted to be circulating in the upcoming season. As a result costs of annual influenza vaccination for CHD combined patients are high and vaccination cost-effectiveness may not be achieved especially in patients with mild disease whose coronary heart event(s) incidence is low and/or may not require intensive care/treatment. However, this need to be carefully considered as influenza infection may be one of the factors that exacerbate underlying cardiovascular conditions. More over viral or secondary bacterial pneumonia may deteriorate the course of infection as well as influenza infection may trigger acute coronary syndrome (ACS).

From the rational explained above, the pharmacoeconomic evaluation (PE) to compare cost utility of influenza vaccination in CHD patients including the subgroup analysis indifferent disease severities, Angina and Cardiac Arrest/Myocardial Infarction (CA/MI), was proposed. The result of this evaluation would be useful to guide the decision of policy maker and/or physician to provide and/or to prioritize influenza vaccination provision to patients who have different heart disease severity especially during the outbreaks when influenza vaccine availability as well as healthcare personal and facilities are limited.

2. Objectives of the study

2.1 To assess lifetime cost utility of influenza vaccination in patients with history of angina and cardiac arrest/myocardial infarction.

2.2 To identify the most efficient cost utility among providing (1) no-influenza vaccination, (2) providing influenza vaccination in patients

with the history of angina, and (3) influenza vaccination in patients with history of cardiac arrest/myocardial infarction

3. Expected Benefits

3.1 Demonstration of the data of cost utility associated with the use of influenza vaccination of patients with existing cardiovascular disease.

3.2 Ability to quantify the impact of influenza vaccination on the health and the proof of cost utility of patients with existing cardiovascular disease.

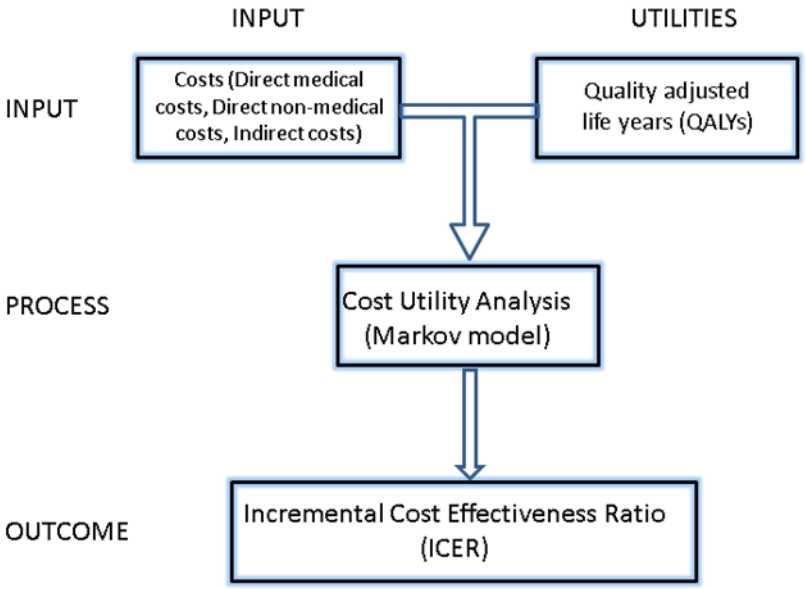
3.3 Suggestion to healthcare professional the economic value of influenza vaccination provided to patients with existing cardiovascular disease.

3.4 The modeling evaluation of cost utility under a range of different scenario relating to different vaccine efficacy/cost, influenza incidence; in both societal and payer's perspective.

4. Scope of the study

This is a cost utility study; therefore, input parameters compose of effectiveness and costs as shown in the Conceptual Frame Work below. The input parameters were entered into the Markov model for processing and the outcome of the analysis is Incremental Cost Effectiveness Ratio.

Conceptual Frame Work of the study



CHAPTER II

LITERATURE REVIEW

This chapter consists of 3 major parts. The first part shows the details of disease information and related pharmacoeconomic studies. The second part shows the concept and details of economic evaluation and the last part shows the related researches in clinical outcomes, cost outcomes, and pharmacoeconomic evaluation.

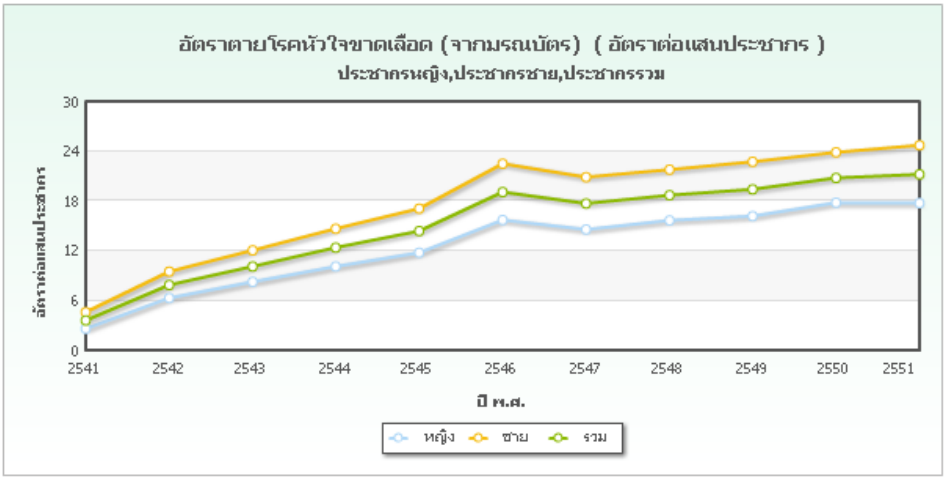
1. Diseases information and related Pharmacoeconomic studies

1.1 Coronary Heart Diseases (CHD)

Nowadays, the CHD burden affects the whole world. Although the death rates of CHD are declining in many developed countries, the rates are increasing in developing countries. Currently, approximately 3.4 million women and 3.8 million men worldwide die from CHD annually. The Global Burden of Disease Study estimated 7.8 million of the 11.1 million deaths due to CHD will occur in the developing countries in 2030.[10]

In Thailand, CHD are the second cause of death. The major cause of cardiovascular disease is the deterioration of artery which leads to arteriosclerosis. This directly affects the narrowing or blockage of the artery at the essential organs in the body such as heart, brain, kidney, and peripheral organ. The most essential are coronary heart diseases which lead to the major cause of death in Thailand.[11] The data from the Health Information System Development Office (HISO) showed the gradually increasing trend of death in CHD patients from 3.6 per 100,000 in 2541 B.E. to 21.19 per 100,000 in 2551 B.E.[12] as shown in Figure 1.

Figure 1 Death rate (per 100,000 population) from coronary heart diseases/ ischaemic heart diseases from 2541 B.E. – 2551 B.E.



Source: Thai Health Statistics 2012. Health Information System Development Office[12]

1.2 Influenza

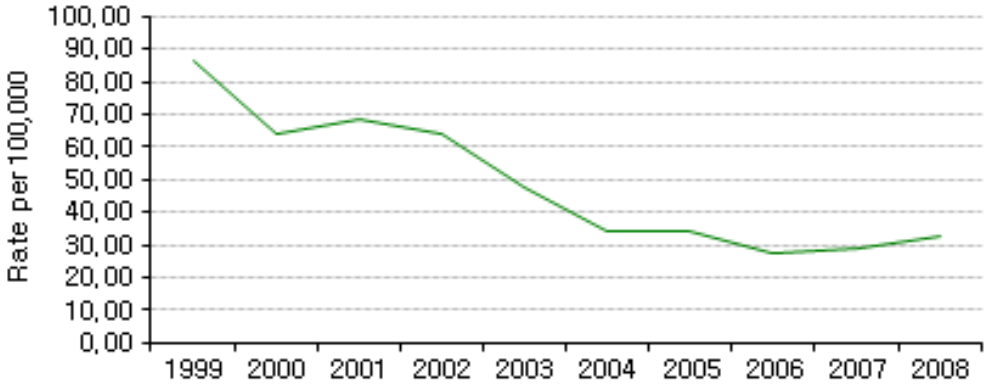
Annually influenza epidemics have the high impact in individual at any age and the utmost risk of complications arise among adults age 65 or older, children under age two, and chronically ill patient of any age who have medical conditions, such as chronic heart disease, blood or metabolic diseases including diabetes, liver, kidney, lung, or, weakened immune systems. Infections may consequence in hospitalization and death mostly among high-risk groups, i.e. chronically ill patients, elderly, or the very young children. The influenza complications may comprise of ear infections, bacterial pneumonia dehydration, sinus infections, and deteriorating of chronic illnesses such as congestive heart failure, diabetes, and asthma. There are consistent reports about association between influenza and acute myocardial infarction (AMI) from numbers of observational studies employ various research methods in different settings.[13] Globally, influenza outbreak cause about three to five millions severe illness incidents, and approximately 250,000 to 500,000 deaths.[14] With the situation that pandemic of specific influenza emerges such as novel 2009 H1N1, a magnificent more people may get sick and require additional hospitalization

and deaths than common seasonal influenza does. Crucial public health and economic difficulties may be initiated by Influenza. In industrialized countries, influenza outbreak can cause massive absenteeism which results in productivity losses. In communities, healthcare facilities would be overwhelmed when enormous patients require treatment during outbreak. For Thailand, a population-based surveillance study was conducted starting from January 2005 through December 2008 to prospectively identify in-patient pneumonia cases with laboratory confirmed influenza.[15] To estimate countrywide yearly influenza pneumonia hospitalization and in-patient deaths, age-specific incidence was calculated and extrapolated. The finding revealed that an essential cause of hospitalized pneumonia in Thailand was influenza virus and yearly approximation of hospitalization and in-hospital pneumonia deaths were about 36,413 and 322, respectively. This is in accordance with a current decision of Thailand Ministry of Public Health (MOPH) to extend annual influenza vaccination to elderly and suggest the target of regular influenza vaccination in children.

In January 2004, there was a status appraisal of influenza surveillance, vaccination, research, and policy which Thailand was modeled as a case study for middle income countries.[16] There were 64–91 clinically diagnosed influenza patients reported per 100,000 persons annually between 1993 to 2002. From 4,305 specimens submitted to the national influenza laboratory, 34% were being able to isolate influenza viruses from the specimens. However, yearly influenza immunization, estimated from vaccine distribution, was less than 1%. The appraisal suggestion that Thailand could be able to take more active steps toward influenza control as the country's economy is growing and has a well-developed public health infrastructure with an effective national immunization program.

In 2008, Bureau of Epidemiology Thailand obtained the influenza case report of 20,881 cases; 33.03 per 100,000 persons which the reported cases were gradually increased after the highest decline in 2005 (Figure 2). There are 2 reported deaths (0.01% of reported influenza cases) but there was no disease investigation report.[17]

Figure 2 Reported Cases of Influenza per 100,000 population, by Year. Thailand 1999-2008



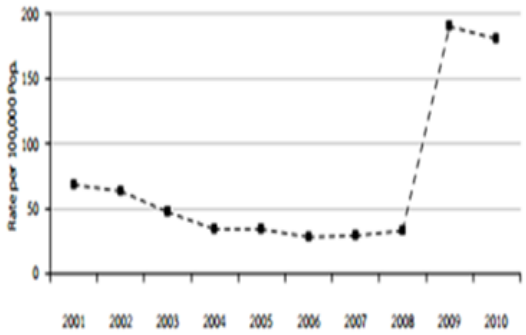
Source: Annual Epidemiology Surveillance Report 2008. Bureau of Epidemiology, Thailand[17]

In 2009, Bureau of Epidemiology, Thailand obtained the influenza case report of 120,400 cases; 189.73 per 100,000 persons. The incidence sharply increased comparing to the passed 3-5 years due to the spread of Influenza A novel H1N1, pandemic strain (Figure 3). There were 231 reported deaths; 0.36 per 100,000 persons (0.19% of reported influenza cases).[18]

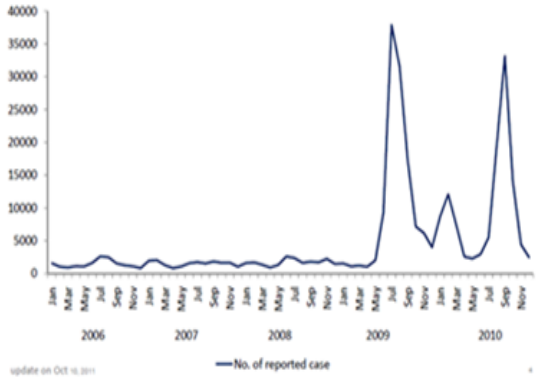
The reported influenza cases were decreased a little in 2010 (Figure 3). In 2010, from the disease surveillance database, 115,183 influenza patients were identified; 180.82 per 100,000 persons. There were 1,206 reported deaths; 0.20 per 100,000 persons or 0.11 accumulated 10-year (from 2001-2010).[19] In 2011, data from January to 5 October, there were 40,133 influenza reported cases with 7 reported deaths. The highest death rate was found in patient aged 55-64 years (0.33 per 100,000 persons).[20]

The recent Influenza incidence described above revealed that influenza is a health problem in Thailand and pandemic can be emerged at any time and therefore emergency strategy should be in place to combat the influenza in a timely manner.

Figure 3 Reported Cases of Influenza per 100,000 population, by Year. Thailand 2001-2010



Reported Cases of Influenza per 100,000 population by Year, Thailand 2001-2010



Reported case of Influenza by month, Thailand 2006-2010

Source: Annual Epidemiology Surveillance Report 2010. Bureau of Epidemiology, Thailand[20]

1.3 Influenza and Coronary Heart Diseases

After influenza pandemic in Europe and the USA in 1900s a possible relation between influenza and higher mortality from cardiovascular events was become aware of.[21] A peak incidence of acute myocardial infarction and stroke were occurred in winter and respiratory and urinary tract infections increased the risk of both events considerably.[22] Considering global enormous burden on morbidity and mortality and future influenza outbreak potential, the cardiac manifestations of influenza infection are suspected to be a significant proportion of deaths from the global 20th century outbreak due to cardiovascular causes. Furthermore, a marked increase in death rates from cardiovascular causes has been observed during influenza epidemics in a number of population and clinical studies.[21]

It was well recognized that influenza infection may cause cardiac complications such as atherosclerosis and myocarditis which was an appropriate explanation of ACS. The consistent evidences that influenza triggers acute myocardial infarction and cardiovascular death were well developed and there are some evidenced demonstrating effectiveness of influenza vaccines in reducing the risk of

cardiac event in cardiovascular patients.[13] However many factors including the age and immunity of vaccinee and the vaccine efficacy influence influenza vaccination effectiveness. Undeniably, matching inactive influenza strains in influenza vaccine with the circulating strains in the community lead to the most influenza vaccination effectiveness. In seasons with a poor match, it has been demonstrated that the reduction in hospital admission and death is smaller than in seasons with a good match.[23]

There was one observational study in Northern of Thailand studying the recent influenza infection evidence occurred prior to acute coronary syndrome among patients hospitalize in a tertiary care hospital. The result revealed that influenza and influenza-like-illness (ILI) prevalence in acute coronary syndrome (ACS) population was about 23% while the influenza and ILI prevalence in general Thai population was only 0.01%. The increase influenza occurrence frequency in ACS patients in winter time was similar to other studies suggesting that ACS may be triggered by influenza.[24]

Influenza vaccination as a preventive measure for ACS is attractive in high risk patients due to influenza vaccines effectiveness, inexpensiveness and wide availability. Reduction in heart disease by influenza vaccination is still not fully established. There is a systematic review attempting to measure the effect size of influenza vaccination in cardiovascular patient and non-cardiovascular patient in the prevention of heart disease. The review noted the significant effect but could not be concluded due to insufficient vaccination data on CHD.[25]

1.4 Influenza Prevention

Influenza vaccination is the most effective measure to prevent the disease or severe outcomes from the influenza illness. Available influenza vaccines are safe and effective and have been used for more than 60 years. Influenza vaccine can prevent influenza-specific illness from 70% to 90% and may reduce severe illnesses and complications by up to 60% and reduce deaths by 80% among healthy adults.[14]

Among elderly, ILI, pneumonia and the risk of death can be reduced by influenza vaccination.[26] Additionally, all cause of death and the risk of heart attack and stroke can be effectively prevented by influenza vaccination.[27] However, the results are likely to be bias due to the nature of observation studies.[28,29]

1.4.1 Influenza Vaccine[30]

Influenza vaccines are a mainstay to substantially reduce the health burden from seasonal influenza. Inactivated influenza vaccines were discovered and have been in use since the 1940s. Influenza vaccines compose of two types:

1.4.1.1 Influenza vaccine injection (IM):

An inactivated vaccine (containing killed virus) has been approved to use in people older than 6 months, healthy people, and chronically ill patients. There are three different influenza injections available

1.4.1.2 Nasal-spray influenza vaccine:

A vaccine composes of live, weakened influenza viruses (Live Attenuated Influenza Vaccine – LAIV). LAIV is approved for use in healthy people aged 2 through 49 years excluding pregnant women. Live attenuated, cold-adapted influenza vaccines (LAIV) were discovered and developed in the 1960s and are administered via nasal spray.

Seasonal influenza vaccines project to combat three influenza viruses that are most common during the upcoming season, based on the current research. The viruses in the vaccine may subject to change annually based on international surveillance and scientists' estimation about which types and strains of viruses that are going to circulate in the coming influenza season. Protective antibodies against the influenza virus will be developed in the body approximately after 2 week after vaccination.[23,34]

1.4.2 Influenza vaccine recommendations

The Bulletin of the World Health Organization (WHO) February 2008 stated that the chance of cardiovascular and cerebrovascular disease suffering is

approximately less than 20% when elderly individuals are given influenza vaccine. In addition influenza vaccine may also decrease mortality risk, from all causes, by half compared to unvaccinated.[31]

WHO[14] and the Advisory Committee on Immunization Practices (ACIP)[6] recommend annual vaccination for:

- Nursing-home residents (the elderly or disabled)
- Elderly individuals
- Children aged 6 months up to 19 years old
- Chronically ill patients at any age
- Other groups such as pregnant women and those with essential functions in society.
- People living with or providing care to those at high risk for complications from influenza, including:
    - Health care workers
    - Household contacts of persons at high risk for complications from the influenza
    - Household contacts and caregivers of children <5 years of age with particular emphasis on vaccinating, contacts of children <6 months of age (these children are at higher risk of influenza-related complications)

More specifically for CHD patients, influenza immunization with inactivated vaccine (administered intramuscularly) is recommended by the American Heart Association and American College of Cardiology recommend as part of comprehensive secondary prevention in persons with coronary and other atherosclerosis (Class I, Level B).[5] This is in contrary with the guidelines of

European Society of Cardiology which declare lack of documented evidence in influenza immunization effects either on the chronic heart failure or stable angina clinical course and also requested placebo-controlled trials.[32,33]

It is the highest priority to expand influenza vaccination to cover high-risk population; therefore, the American Academy of Family Physicians now recommends yearly influenza vaccination in all people 50 years of age, to replace its previous recommendation that cover only people aged 65 and older. The new aged group is subject to high morbidity and mortality rates associating with influenza which lead to cost-effective in vaccination.[34]

For Thailand, NHSO provides influenza vaccination to high risk patients (7 chronic diseases: chronic obstructive pulmonary disease, asthma, heart disease, cerebrovascular disease, renal failure, diabetes mellitus, and cancer receiving chemotherapy). The influenza vaccine is provided to decrease the risk of severe influenza. In 2010 1,536,664 influenza vaccine doses were provided to target population (high risk group and elderly. However the disease severity is also not included in their provision consideration.[9]

1.4.3 Influenza Vaccine Safety

Influenza vaccine safety is higher than therapeutic medicine as shown by independent experts and WHO; however, vaccine safety receives more public attention than its effectiveness.[31] Now a day, it has been shown that most influenza vaccine scares are false alarms as an excellent safety record of influenza vaccines have been recorded.[35] The previous misguide about safety concerns have led to a reduction of vaccination coverage in some countries.

Sore arm and redness at the injection site are the most common adverse events associated with inactivated vaccines while systemic symptoms such as fever or malaise are less common in vaccine safety report. There is a rare case of other event which was not included in this review. The most common adverse events from LAIV are nasal congestion, headache, myalgia or fever. The increased risk of wheezing was observed in some young children enrolled into clinical studies. As a result, LAIV is

not recommended for children younger than 2 years old. LAIV is also not recommended for children ages 2-4 old whose history of recurrent wheezing or reactive airways disease is existed or old chronically ill patient whose increased risk of influenza-related complications are presented.[34,36]

2. Economic Evaluation

2.1 Economic Evaluation Concept

Rapid in healthcare costs escalation and resource limitation have direct to augmented emphasis on evidence-based medicine such as economic evaluation modeling to evaluate the clinical and cost–effectiveness in comparison to alternative therapeutic strategies. Economic modeling is one of the highly efficient tools for economic evaluation. It is a method to signify the complexity of the factual world in a basic and intelligible form using mathematical and/or statistical association. The recent and under developing roles of modeling in health economic evaluation include development of the analysis, interpretation and generalization of the analysis. It also includes the use of modeling to design and to prioritize future trials.[37] When confronting situation that the trial data is unobtainable for ethical, political, or cost reason, economic modeling is crucial. However to assembling an economic model for influenza vaccination evaluation in patients with existing cardiovascular diseases, to maximize both internal and external validity and ensuring that the underlying assumption are appropriate is important. By doing this data from evaluation will be creditable and will be well accepted for generalization.

To evaluate if the information incorporated into the model is either low quality or entirely lacking is also the highlights areas for being transparent.[38] Sensitivity analysis will be applied comprehensively to evaluate the robustness of the results attained when data is insufficient. Comprehension of the results robustness and specific areas when data are either limited or entirely missing will also be worth in acknowledging future research prioritization and to focus on the key manipulating variables to the pharmacoeconomic evaluation.[39]

For Thailand, the recent health system management has increased the emphasis on health expenditure due to the limitation of health resources and budget. The health management, therefore, focuses on the most efficient resource allocation. As a result, health assessment is used as a useful tool for decision makers in health policy and Thai Health Assessment Technology guideline was developed and disseminated in 2009.[40]

2.2 Type of Economic evaluation

Health economic evaluation means comparative evaluation between costs and outcomes of technology on health. Drummond et al. divided health economic evaluation into 6 types as follows:[41]

Evaluation of one option only with no comparison.

2.2.1 Outcome description: evaluate only health outcomes

2.2.2 Cost description: evaluate only costs.

For Thailand only cost consideration is the most popular evaluation in the past decade and it is believed to be a solid foundation for the future health economic evaluation.

2.2.3 Cost-outcome description: evaluate both health outcomes and costs.

Evaluation by comparing the two types of options or more

2.2.4 Efficacy/cost-effectiveness study: evaluate clinical efficacy or effectiveness among alternatives.

2.2.5 Cost analysis: evaluate only cost among alternatives

2.2.6 Full health economic evaluation: evaluate both cost and health outcomes by comparing among 2 alternatives or more. Full health economic evaluation will present appropriate information for decision making in health policy.

Full economic evaluation composes of 2 parts, cost and outcome of two comparative alternatives or more. Cost will always be measured in economic unit while outcomes will be measured or evaluated in clinic or economic unit or utility. Thus full health economic evaluation can be divided into 4 methods as follows:

2.2.6.1 Cost-minimization analysis (CMA)

CMA is a method to compare alternatives with the same/equivalent outcome or assume to be equivalent or the difference is not statistically significant; therefore, only the cost is different. CMA is considered as a suitable health economic assessment because CMA can identify the alternative with the lowest cost. However Drummond et al. suggested that CMA no longer be considered as a completed health economic assessment since it is difficult that the outcomes of any alternatives are equivalent. Later on Briggs and O'Brien[42] supported that it is very rare to identify situation suitable for CMA as there is no study that decided to prove the equivalence of different treatments. As a result CMA is not recommended.

2.2.6.2 Cost-benefit analysis (CBA)

CBA is a method to measure alternatives' costs and outcomes and make comparison in the monetary unit. All outcome units will be transformed to monetary unit for comparison. In theory CBA is an absolute benefit of each alternative or to assess the outcome by comparing resource utilization. Therefore CBA can be used to compare alternatives with the different objective such as the analysis of anti-hyperlipidemia and avian flu vaccination. However CBA is not wildly used in health economic assessment as some health outcome cannot be transformed to monetary unit or transformation may contradict to the generally acceptance.

2.2.6.3 Cost-effectiveness analysis (CEA)

CEA is a method to compare alternative whose effectiveness or clinical efficacy is different. Costs will be calculated in monetary unit and the outcome will be measured in clinical unit such as decrease in blood pressure, number of patients cured, or life year gained. CEA is the most common health economic assessment method.

CEA has the objective to provide information for decision aiming to maximize health outcome under resource limitation. However there is a debate if effectiveness of efficacy data should be used. In general CEA is used to compare alternatives with the same unit such as life-years gained from cancer treatment. Moreover CEA can be used to compare alternatives with the different objectives such as to compare antihypertensive medicine and anticancer medicine with the same outcome such as life-years gained.

2.2.6.4 Cost-utility analysis (CUA)

CUA is used for health economic assessment by measuring utility. Utility reflects individual's preference to the outcome. Quality of life is an example of CUA; therefore, CUA provides completed information as it includes qualitative and quantitative outcomes. Generally CUA is perceived as the further analysis of CEA by adjusting the quality of CEA's outcome. For example life-years gained from anticancer treatment are adjusted by utility of patients' preference to that health status. The outcome will be quality-adjusted life years which is the common outcome of CUA.

Cost utility analysis and Cost effectiveness analysis are very similar that have a common goal to maximize health outcome from limited resource. Some economic articles use these terms interchangeably. Actually CUA compares alternative outcome in both quality and quantity that allow CUA to compare alternative with many outcomes as CUA combines quality and quantity in one outcome. As a result CUA can compare largely different alternatives. The result of CUA is QALYs gained therefore CUA requires the final result which is the quality of life. Other result for CUA is disability-adjusted life years (DALYs) developed by World Health Organization. Though the concepts of DALYs and QALYs are similar the formula to calculate are different.

2.3 Cost Estimation Concept

Measuring costs in health care is a value estimation of limited resource such as medicine, supplies, medical equipment, physician's time, patient's time, etc. They are

healthcare intervention lead to health outcome. Cost estimation is used for economic burden of the illness. Economic evaluation or outcomes research are used to arrange priority for policy and planning

There are 3 types of costs

2.3.1 Direct medical costs: resources used for the measure of health which covers costs of diagnosis, treatment, follow-up, recreation and end-stage care. These cares may occur in or outside healthcare facilities.

2.3.2 Direct non-medical costs: the out-of-pocket expenses for goods and services that are not medical/healthcare service such as costs of travelling, food, facilities, informal care and service.[43]

2.3.3 Indirect costs: lost productivity due to illness of death that may or may not directly paid for the production. For example, productivity lost due to illness absenteeism, permanent disability, or premature death.

2.4 Utility/Quality of Life[44,45,46,47,48]

Utility is value or worth given to health status or improvement of health status by assessing preferences of individuals or society. Utility can be used to calculate quality adjusted life year (QALYs) which are the most used outcome of cost utility analysis. The number of QALYs is calculated from the life expectancy multiply by utility scores. In general utility scores are in the range of 0 (death) and 1 (perfect health). However utility score may be less than 0 that means health status is worse than death.[49]

Many diseases have impact both patients' life expectancy and health-related quality of life (HRQOL) that cannot be obtained from clinical outcomes or laboratory results. HRQOL assessment is essential to know the impact of the disease and treatment to patients from patient's perspective. HRQOL is a construct composed of many health concepts such as physical health, mental health, social health, and general health. There are 2 HRQOL assessment instruments which are:

a) Generic instrument: no age-, gender-, and disease-specific

b) Specific instrument such as disease-specific instrument and age-specific instrument.

HRQOL assessment instrument reports scores in 2 categories:

a) Profile scores: reports scores by domain of the instrument

b) Index scores/utility: reports score in single number between 0-1. Generally 0 means death and 1 means full health. Utility can be used to calculate quality-adjusted life years or QALYs which is the important health outcome and is widely used in cost utility analysis.

There is no conclusive concurrence on the definition of HRQOL though its extensive use of the term. It generally refers to physical, emotional and social well-being. It provides a mutual standard which can be assessed the effect of varied experiences and remedies for the same ailment or the effect of diverse treatments across varied circumstances. Therefore, HRQOL can be termed as health condition and regarded as progressively complex range of patient outcomes that include physiological, functional and overall wellbeing or quality of life.[50]

2.4.1 Utility measurement

Sometime value or preference term is used for utility. Actually these 3 words are different. Preference is the concept composing of utility and value. There are 2 essential considerations in utility measurement as follows:

2.4.1.1 Type of questions

a) Question for certain health outcome: probability is not be involved. Responders compare 2 or more outcomes and then select the preferred outcome or give scores to all outcomes.

b) Question for uncertain health outcome: Responders compare outcomes of 2 alternatives which one alternative has probability involved.

The differences of those 2 types of questions are that the certain outcomes do not have the risk attitude of the responders while the uncertain outcome should consider the risk attitude in 3 types, Risk averse, Risk seeking, and Risk neutral.

In the real world health outcomes are uncertain. Therefore utility measurement using of questions for uncertain outcomes is more appropriate.

2.4.1.2 Type of answers

a) Scaling: scoring based on psychometric scaling

b) Making a choice: scoring based on economic and decision sciences.

The making a choice is more wildly used by the most researcher than the scaling.

2.4.2 Utility methods

2.4.2.1 Directly measured utility methods

a) Visual analogue scale (VAS): utility measured by rating based on the integration theory explaining cognitive process of judgment. This theory has 2 constructs, integration and valuation. VAS asks responders to score their health on the responding day. VAS scale may be presented in vertical or horizontal by which 100-score upper bound means perfect health and the 0-score lower bound means death. Utility score will be calculated by dividing VAS by 100. VAS is the simplest directly measured utility method and does not require long time to respond which gives advantage to responders who do not have much time.

b) Standard gamble (SG): SG is based on the decision under uncertainty and is the original method of utility measurement. In SG responders have to decide whether or not to choose treatment that has risks to cause death (treatment failure) or cure/becoming healthy (treatment success). Utility will be calculated from probability or percentage of treatment cure and acceptance of responders to choose that treatment.

c) Time trade-off (TTO): TTO theory is interesting and similar to the concept of QALYs. TTO was developed as an alternative beyond SG which is difficult for responders to understand the probability.[51] By TTO method responders will be asked to choose between live in bad health status in (t) duration or to live in good health in the shorter time (x).

2.4.2.2 Other directly measured utility methods

Time trade-off (TTO): TTO is the assessment of social value for a certain health status. The responders will choose alternative related to the others not themselves. TTO is suitable for resource allocation but TTO provides significantly different utility than the VAS, TTO, and SG.

2.4.2.3 Indirectly measured utility methods: this is a multi-element health status classified system comprising 2 steps. At the first step, responders are self-assessed their health status using health-related quality of life tools that compose of various domains such as mobility, pain. Then utility at each domain will be calculated from self-assessment using regression developed from utility directly obtained from the population explored previously. The well-known methods of this measure are as follows:

a) Quality of well-being (QWB): composes of 4 domains; mobility, physical activity, social activity, and symptom-problem complex.[52] Mobility and physical activity compose of 3 topics, social activity composes of 5 topics, and symptom-problem complex composes of 27 symptoms.

b) EuroQoL (EQ-5D): composes of 5 health dimensions, mobility, self-care, usual activity, pain/discomfort, and anxiety/depression. Each dimension has 3 choices, no problem, moderate problem, and severe problem. Equation used for calculation was developed from the utility data from TTO method in randomly selected 3,000 general adult populations from UK.[53] Utility scores calculated by this method will be between -0.59-1.00. Timing for EQ-5D will be about 1 minute and the questionnaires have been translated into many languages including Thai.

c) Health utilities index (HUI): Mostly used HUI are HUI2 and HUI3. HUI2 was firstly developed for young cancer patients and was further adjusted for adult used. HUI2 composes of 7 health dimensions as follows: sensatory, mobility, emotion, cognition, self-care, pain and fertility. Each dimension has 4-5 choices from worst to normal. Equation for utility score calculation by this method was developed from utility data using VAS and SG method conducted in Hamilton, Canada population. Calculated utility scores are between -0.03-1.00. HUI3 is similar to HUI2 but it does not include fertility dimension and sensation domain was expanded to 3 dimensions; vision, hearing, and speech. Each dimension has 5-6 choices. Equation for utility score calculation was developed from utility data using VAS and SG method conducted in adult population in Hamilton, Canada. Equation for HUI3 was mostly updated using SG by which utility scores calculated by this method are between -0.36-1.00. Timing for responding to questionnaire is 10 minutes and 2-3 minutes by interview method.

d) Short form six-dimensions (SF-6D): SF-6D was revised from SF-36 questionnaire composing of 6 dimensions, physical functioning, social functioning, role-limitations, vitality, mental health, and pain. Each dimension has 4-6 choices. Utility scores were derived from SG in 611 representative populations in UK. Utility scores are between 0.29-1.00. SF-6D can assess the utility from SF-36 data by regression. There is other method to assess utility from SF-36 by regression such as Nichol's method and Fryback's method. These two methods were developed from US population data.

2.4.2.4 Other methods for deriving utilities

a) Expert opinion: expert opinion should be used when utility data are not available or utility is not the primary variable in the analysis. Obtaining utility data from expert opinion should be done by the standard method such as Delphi method which the answer is the agreement from the expert group.

b) Forecast utility of SG or TTO from VAS: VAS is a simple instrument and is not a time consumed in utility assessment comparing to SG

or TTO. Therefore there is an attempt to forecast SG or TTO utility from VAS. George Torrance found that scores measured by VAS, SG, and TTO have power curve relationship.[54] However other researchers found relationship in other patterns which are more appropriate than power curve relationship.[55] As evidence cannot certainly confirm the relationship among VAS, SG, and TTO; therefore, utility of SG or TTO should be accessed directly rather than forecasted from VAS.

c) Willingness to pay (WTP): WTP is another method which can be used to assess utility scores of the health-related outcomes. WTP can be used to assess health value by showing in economic unit and can be used for cost benefit analysis.

The most commonly used scaling techniques for utility assessment are the SG, TTO, and the rating scale (RS). Multiple studies have shown that for a given health state, SG, TTO, RS produce different scores. Because the cost effectiveness ratio may vary according to the choice of the scaling technique, the choice of the scaling technique is an important methodological issue. There is no consensus so far on which scaling technique is the most appropriate to use. This probably reflects the fact that none of these scaling techniques is perfect. As reported previously, SG assessment is based on a solid theory. In addition, it measures the respondent's preference for health state under conditions of uncertainty. When medical decisions involve uncertainty, SG may assess preferences in a more realistic fashion than the non-risky preference-based measures. However, the feasibility of administering such a complex instrument has been questioned by many. Compared to the SG, TTO is easier to administer. In addition, TTO directly measures the number of healthy years that are equivalent to a given time in a particular health state. In other words, it directly tests the willingness of the respondents to given up years of life in exchange for a better HRQOL, which is the foundation of the QALY model. The RS is the easiest technique to administer. However, it produces interval-level measures only when the respondents are instructed that the intervals between the locations of the different health states reflect the difference they realized among the health states. Recently, the US Panel on Cost-Effectiveness in Health and Medicine suggested that preference-based techniques be used to assess quality weights. They suggested that

when results are based upon measurement techniques such as the RS, they should be compared with results obtained using the TTO and the SG. However, a review of the cost-effectiveness analyses published between 1975 and 1995 (n=80) reported that only 5% and 18% used the SG and TTO scores, respectively, as quality weights for QALY analyses. This may reflect the difficulty of using complex instruments such as the TTO and SG scaling techniques.

Compared to the TTO and the SG, the RS was the most highly correlated with the different aspects of the HRQOL measured by the Short-form 36 Questionnaire (SF-36) Health Survey and had the highest ability to discriminate CHD patients with various physical disabilities and participants reporting specific number of health problems.

HRQOL of patients with CHD may be affected by the nature and severity of the disease, and the adverse effects of treatment. Almost every aspect of the HRQOL can be affected by CHD. For example, in the Medical Outcomes Study, patients with a previous myocardial infarction reported lower physical, role and social function, as well as lower scores on the mental health, health perception and bodily pain subscales when compared to individuals without chronic conditions. The SF-36 Health Survey has been validated in general and in various patient populations, and used in CHD treatment and prevention.

To be used as a quality weight in a cost-effectiveness analysis, A HRQOL measure needs to fulfill some minimal requirements. First, the HRQOL of each health state should be represented by a unique score. Second, in order to be able to compare the cost-effectiveness of different programs, the quality weight should be measured on a universal scale that can accommodate all possible health states. By convention, analysts use scales which range from zero to one, representing death and perfect health, respectively. Finally, the quality weights should be measured on at least an interval scale in order to be used in mathematical operations. An interval scale is characterized by an equal distance between the scale points and by an arbitrarily selected zero point.

HRQOL can be assessed by using either a non-preference-based or a preference-based approach. The non-preference-based approach consists of desorbing various aspects of the HRQOL, for example, by asking questions about the presence, the severity and the frequency of symptoms or the ability to perform daily tasks. The SF-36 health survey is an example of a non-preference-based HRQOL: general health perception, physical functioning, role limitations due to physical health problems, and role limitations due to emotional problems, social functioning, bodily pain, vitality, and general mental health. The general health perception subscale represents an overall evaluation of health. However, this subscale does not provide interval scale data and is not preference weight. For these reasons, its results cannot directly be used in cost-effectiveness analysis.

The preference-based approach consists of asking the respondents to make a judgment about the value of life with a given health state. It measures the strength of the preference for health conditions Preference-based measure are currently used in cost-effectiveness analyses as quality weights because they provide a single HRQOL score for each health state measured on a universal and interval scale. In addition, they are particularly useful in allowing allocation of resources in accordance with a population's judgment about a range of health states.[56]

2.4.3 Concept of quality adjusted life year (QALYs)

Health Outcome can be distinguished into 2 dimensions, life expectancy and quality of life and QALYs are the integration of these 2 dimensions. Many diseases impact not only patient's life expectancy but also patient's quality of life. Calculation of QALYs has advantage as it combines both benefit and disadvantage from treatment in the same unit.

Calculation of QALYs

$QALYs = (year_t \times \text{quality of life}) + (year_{t+1} \times \text{quality of life}) + \ldots \text{Until death}$

2.4.4 Quality of life in patients with coronary heart disease

The assessment of quality of life as an indicator for health outcome in coronary heart disease (CHD) patients has been speedily and meaningfully increased. There are various features where CHD patients' quality of life, in clinical course, may be influenced. CHD patients have limitation for exercise competence, physical incapacity, and mental hassle related to continuing pressure includes symptoms of angina and heart failure. Recent treatments currently emphasis not only on expanding life expectancy, alleviating symptoms and enhancing functional status, but also enriching quality of life. Thus, it is important to consider health-related quality of life (HRQOL) as a primary outcome to ascertain therapeutic advantage.[57,58]

It is crucial to select appropriate health dimension measures relevant to particular group of patients when measure their HRQOL. It should be taken into contemplation the individual's responses to live with the illness as well as the acute and chronic physical disease outcomes when selecting the instrument measure as all almost aspects of patient's life may be affected from illness.[59]

The differences (from normal population) in both psychological and somatic features of quality of life after 1 month of AMI event were revealed in a prospective controlled study. The difference still exists within one year after the predominantly in somatic symptoms; however, the differences are non-significant across patient groups. There were reports from patients soughing emergency out-patient care during the follow-up year for clinically diagnosed angina pectoris or cardiac incompensation demonstrating higher level of thoracic pain ($p < 0.001$) and breathlessness ($p < 0.001$) at 1 month follow-up compared to patient who did not seek such care.[60]

The case series study in ambulatory cardiology clinics at tertiary care medical centers to assess angina pectoris patient's attitudes concerning symptoms revealed that the mean attitudes followed the anticipated patterns (those with more severe Canadian Cardiovascular Society scores have lower utilities).[8] Attitudes concerning symptoms diverse extensively among patients with correspondingly severe angina. The study summarized patient utilities by measurement metric and Canadian Cardiovascular Society (CCS) class as assigned by the patient's cardiologist. The study result can be concluded that Angina patients with comparable functional

imperfection varied noticeably in their utilities and recommended disease management guideline in ischemic heart patient based on individual's utility rather than on symptom severity only.

Regarding alteration of utility of over time, there was a study conducted in myocardial infarction survivor and the result revealed time-tradeoff utilities for all patients was 0.88, 95%CI 0.84 to 0.93. In addition over a mean interval of 8.4 month, time tradeoff scores remained stable, with a mean change of 0.03, 95% CI -0.02 to 0.08; p = NS.[61]

2.5 Markov Model of Coronary Heart Disease

Weinstein et al., Harvard University, constructed Coronary Heart Disease Policy Model[62] which is a state-transition comprising 3 major sectors: the Demographic-Epidemiologic Model (DE Model), the Bridge Model, and the Disease History Model (DH Model). Each year the model incorporates new 35-year old persons and removes patients who die or survive at age 85. DE model identify new CHD cases whom are entered the Bridge Model where the first month with disease is described. The Bridge Model combines these new CHD patients with other existing CHD (prevalence).

The CHD model[63] developed by Health, Social, and Economics Research component of Health is an abbreviated version of the Coronary Heart Disease Policy Model developed at Harvard University by Weinstein et al.[62] The model was simplified by eliminating the states related to coronary artery bypass graft surgery as well as combining the Cardiac arrest (CA) and Myocardial infarction (MI) states into a single state. As a result, the model includes four CHD states: Normal, Angina, History of CA or MI, and Death. Due to the very low survival rates associated with CA, the transition probabilities given a history of CA/MI are those given a history of MI; however, mortality rates associated with CA are incorporated as appropriate. Most of the probabilities in the model are derived from the probabilities outlined by Weinstein et al (1987)[62] and its updated version in Hunink et al. (1997).[64]

2.6 Uncertainty analysis

The result from Model-based cost-effective analysis may vary depending on the estimation of the cost and effectiveness. The uncertainty may be sensitive to the assumptions and values of the variables used in the model. The analysis

3. Relevant Research

3.1 Influenza vaccine effectiveness studies in coronary heart diseases

The effectiveness of vaccination in patients with cardiovascular diseases is mainly derived from epidemiological evidence which showed that those patients with congestive heart failure and other cardiac diseases are associated with excess mortality during influenza epidemics. Three case-control studies performing during the 2004-2005 influenza season in the elderly from 64 years old of age in Spain revealed that influenza vaccination significantly decreased the hospitalization risk during influenza season. The adjusted odds ratios for ACS, cerebrovascular accident (CVA), and pneumonia were 0.13 [p = 0.013], 0.07 [p = 0.007], and 0.31 [p = 0.005], respectively.[65] Other cohort study conducted in all community-dwelling individuals aged from 65 years old diagnosed with chronic heart disease (including hear failure or coronary artery disease) between January 2002 to April 2005 showed association between influenza vaccination and a significant reduction, 37%, in the adjusted risk of mortality during winter from 2002-2005. The results showed advantage from influenza vaccination and supported a yearly vaccination strategy in elderly cardiac diseases patients.[66]

An analysis of the cardiovascular mortality (ischemic heart disease, cerebrovascular diseases, and external causes) before and after the influenza vaccination commencing in Brazil showed the similar inclines of regression lines for cerebrovascular diseases (p = 0.931), and external causes (p = 0.941); yet a significant incline of regression line of ischemic heart disease was observed in post-vaccination period compared to the pre-vaccination period (p = 0.022). A significant alteration in the trend towards mortality after 1996 was found for the ischemic heart disease (p =

0.022) but remained unchanged for the cerebrovascular diseases (p = 0.931) and external causes (p = 0.941).[67]

These results highlighted the benefits of influenza vaccination and in accordance with the attempts to enhance the rates of influenza vaccination among elderly. As a result, experts from Texas Heart Institute and University of Texas provided opinion on biological therapy that influenza vaccination is an extremely cost-effective method of cardiovascular protection and are recommended for all patients with cardiac diseases; however, vaccine is largely underused in these patients. Therefore, the experts suggested that increased efforts should be directed towards educating physicians and patients about the benefits of influenza vaccination in coronary heart disease patients.[68]

The results from a retrospective, population based study assessing influenza vaccine effectiveness in the prevention of hospital admission in persons aged over 50 years showed the relationship between influenza vaccination and the lower risk of hospital admission for pneumonia and influenza; this occurred even prior influenza season, apparently due to unmeasured confounding. During influenza season, the relationship between hospital admission and influenza was intensified yielding an adjusted vaccine effectiveness (VE) approximately 12.4%, 95% CI 1.6 to 22.0); 8.5%, 95% CI 3.3 to 13.5 in persons aged from 50-64 and aged 65 years and older, respectively. Result in hospitalizations for ischemic heart disease (IHD), congestive heart failure (CHF), cerebrovascular disease (CVD), or trauma was not significant.[69]

The results from a cohort of 3 large managed-care organizations conducted in community-dwelling members who were at least 65 years old during the 1998–1999 and 1999–2000 influenza seasons revealed the relationship between influenza vaccination against influenza and a decline in the hospital admission risk for cardiac disease, cerebrovascular disease, pneumonia or influenza, and the risk of death from all causes throughout the study period. The results were consistent across all subgroups corresponding age and the presence or absence of key health condition.[70]

The result from a population based case-control study investigating relationship between influenza vaccination and a risk reduction of out-of hospital primary cardiac arrest (PCA) which is a main contributor to cardiovascular death in the community reveal relationship between influenza vaccination and a PCA risk reduction (odds ratio 0.51, 95% CI 0.33 to 0.70).[71]

Randomized controlled trials: Data from published systematic analysis identified 2 original RCTs – FLUVAC and FLUCAD. The FLUVAC study[72] consisted of two randomized controlled trials (FLUVAC MI and FLUVAC PCI), however, they were described as one trial. The study demonstrated 2% death occurrence (primary outcome) in vaccination group compared with 8% in control group which accounted for relative risk 0.25, 95% CI 0.07 to 0.86; p = 0.01. The triple composite end point occurred 11% in vaccination group compared with 23% in controls (p = 0.009).

The second RCT, FLUCAD study[73] revealed cardiovascular death (Primary endpoint estimated 12-month cumulative event rate) at 0.63% in vaccination group compared with. 0.76% in controls, HR 1.06, 95% CI 0.15 to 7.56; p = 0.95. The first secondary composite endpoints, the major adverse cardiac events (MACE: cardiovascular death, myocardial infarction, and coronary revascularization), likely to less frequently occur in vaccination group compared to placebo with the event rate 3.0% and 5.87%, respectively (HR 0.54, 95% CI 0.24 to 1.21, p = 0.13). The second composite endpoints, Coronary ischemic event (MACE or hospitalization for myocardial ischemia - estimated 12-month event rate was significantly inferior in the vaccination group demonstrating 6.02% compared to 9.97% in controls (HR 0.54, 95% CI 0.29 to 0.99, p = 0.047).

The pooled analysis results from these two RCTs revealed 11 and 28 cardiovascular death in placebo treated controls (risk ratio (RR) 0.39, 95% CI 0.20 to 0.77). AMI occurred 16 times in the vaccination group and 19 times in placebo group (RR 0.85, 95% CI 0.44 to 1.62).[25]

In Thailand, the results from a prospective randomized open with blinded endpoint (PROBE) study revealed less frequent occurrence (9.5%) of the primary endpoint (combined major cardiovascular events, death, hospitalization from ACS, hospitalization from heart failure, and hospitalization from stroke), in the vaccination group compared with control group (19.3%). The unadjusted HR was 0.70, 95% CI 0.57 to 0.86; p = 0.004. Results also demonstrated no significant difference in cardiovascular death between influenza vaccination (2.3%) and control groups (5.5%) with unadjusted HR 0.39, 95% CI 0.14 to 1.12; p = 0.088.[74]

3.2 Pharmacoeconomic Evaluation (PE) of Influenza Vaccination

There was no PE specifically in coronary heart disease patients; therefore, PEs in other patient groups were reviewed.

Cost Utility evaluation of Influenza vaccine

Cochrane and Medline were used to identify cost utility evaluation of influenza vaccine. The key words (Title/Abstract) were used as follows:

a) "cost-effective" and "influenza vaccine": 64 results, 19 results were cost utility evaluation of influenza vaccine.

b) "influenza vaccine" and "economic evaluation" and 5 results were found; 1 result was repeated the 1st search and only 2 results were cost utility evaluation of influenza vaccine.

c) "influenza vaccine" and "cost" and "evaluation": 16 results were found; 5 results were repeated and 2 results were cost utility evaluation of influenza vaccine.

d) "influenza vaccine" and "economic": 15 results were found and no result was cost utility evaluation of influenza vaccine.

e) "influenza vaccine" and "utility": 5 articles were found; 2 results were repeat and there was no result was cost utility evaluation of influenza vaccine.

f) “influenza vaccine” and “cost” and “QALY”: 11 results were found, 9 result were repeated and 2 results were cost utility evaluation of influenza vaccine.

g) “influenza” and “utility” and “immunization” and “cost”: 4 results were found; 2 repeated and 1 was cost utility evaluation of influenza vaccine.

h) “influenza” and “QALY”: 45 results were found; 10 repeated and 11 were cost utility evaluation of influenza vaccine.

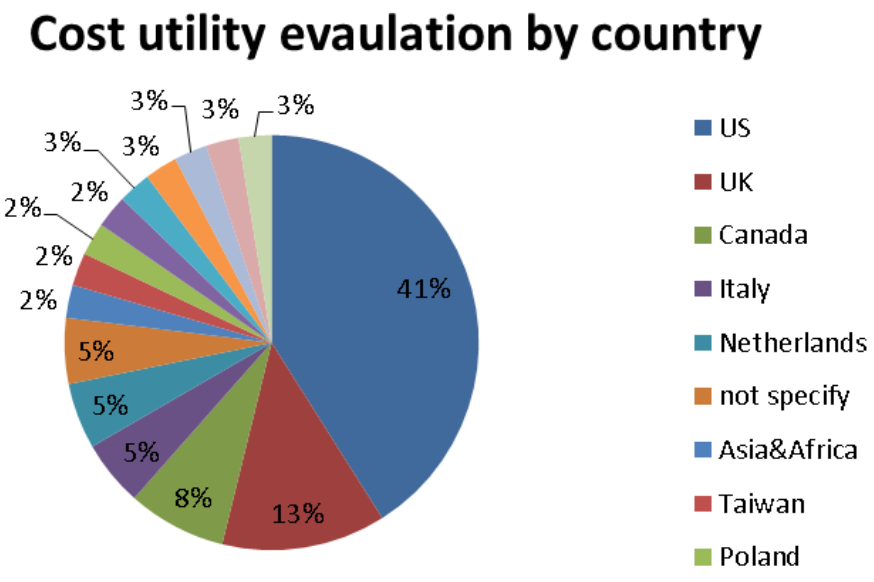
i) Linked from other Pharmocoeconomic studies: 2 results were cost utility evaluation of influenza vaccine.

j) In total, 39 cost utility evaluations were found and reviewed.

The summaries are:

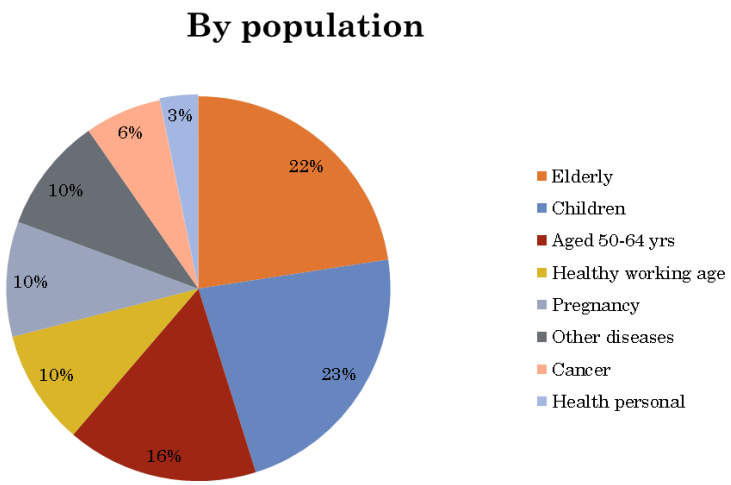
a) By country conducted: 16 studies in US, 5 studies in UK, 3 studies in Canada, 3 studies in Italy, 2 studies in Netherlands, 1 study each from Asia & Africa, Taiwan, Poland, Russia, Australia, Japan, Spain, 1 study international, and 2 studies did not specified country.

Figure 4 Cost utility evaluations demonstrated by country conducted



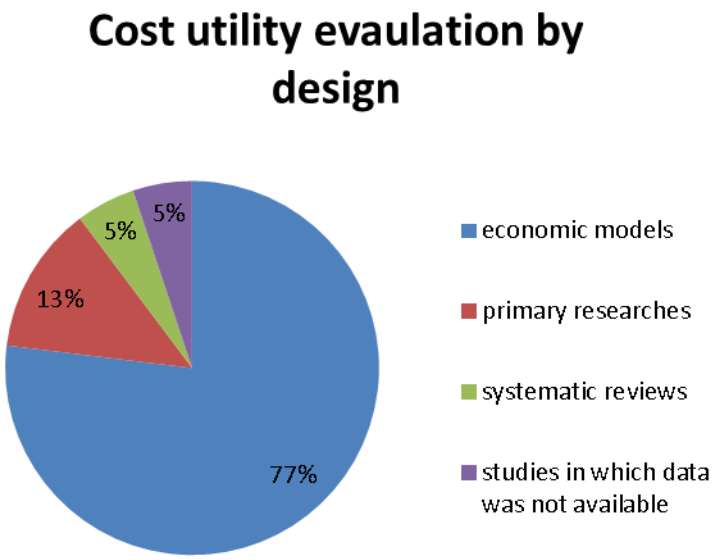
b) By patient group: 7 study in elderly, 7 studies in Children, 5 studies in aged 50-64 years, 3 studies in (healthy) working age, 3 studies in pregnancy, 2 studies in cancer, 1 study in health personal, 8 studies were not specific, 3 studies with other diseases.

Figure 5 Cost utility evaluations demonstrated by population group



c) By study design, there were 30 economic modelings (3 Markov models), 5 primary researches, 2 systematic review, 2 studies that data was not available.

Figure 6 Cost utility evaluations demonstrated by design



d) There is one study evaluating life-time and another one evaluating Muli-year of 5 influenza seasons. The rests were either 1 year evaluation or do not specify evaluating duration and they were assumed 1 year evaluation as the influenza vaccination is provided annually.

From the review specified above, there has been no economic evaluation of influenza vaccination specifically in coronary heart disease patients. Moreover, there influenza is no economic evaluation, to-date, in influenza vaccination that incorporate other disease progression along with the influenza infection

CHAPTER III

METHODOLOGY

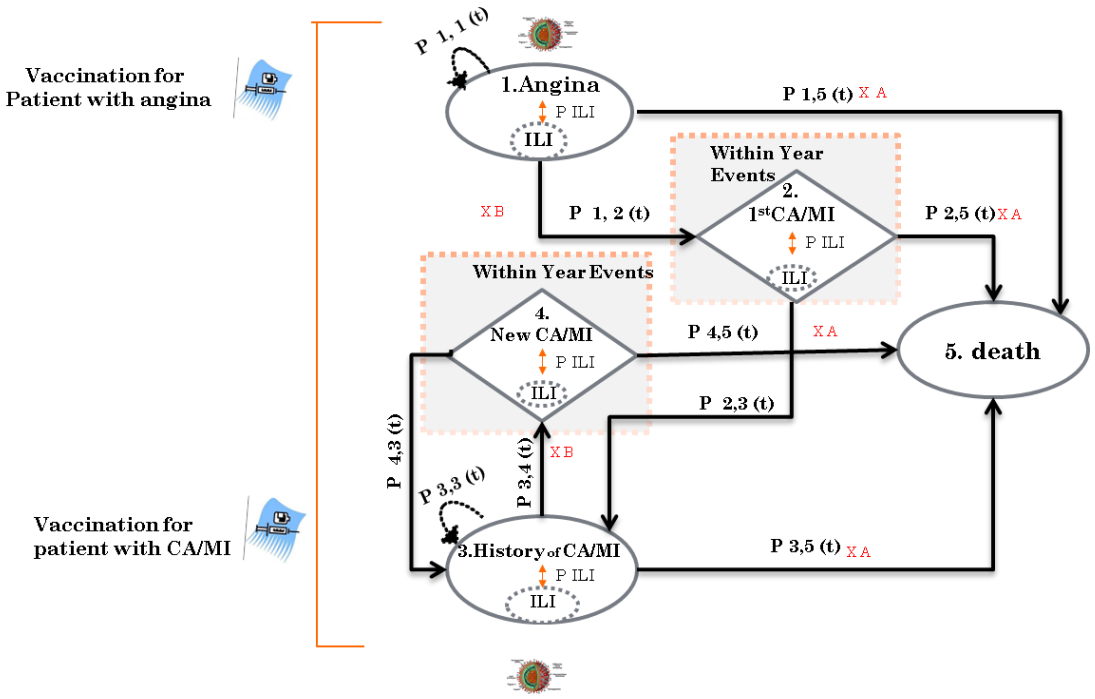
This chapter provides the description of the methodology including the model of the study, cost model, probability of coronary heart disease progression, effectiveness of influenza vaccination, utility, and cost-effective. This research is a Cost utility analysis (CUA) of influenza vaccination in cardiovascular diseases; therefore, input parameters compose of effectiveness and costs of cardiovascular diseases and influenza. The Markov model was applied to this study. Details of modeling technique, types and sources of data input, and model analysis were included in each section of this chapter. The analyses were performed from a societal perspective and study analyses were reported in terms of incremental cost, incremental Quality Adjusted Life years (QALYs), Life Year Gained (LYG), and incremental cost-effectiveness ratio (ICER) per QALY gained and LYG.

1. Model of the study

The Markov model was applied to this study. The coronary heart disease components of the model and the movement probability between states were adopted from a Markov Model of Disease Progression and Cost-effectiveness of Coronary Heart Disease for Type 2 Diabetes[63] which is an abbreviated version of the Coronary Heart Disease Policy Model developed at Harvard University[62] but our study model starts with patients with a history of coronary heart diseases either Angina or CA/MI and influenza infection (adopted surrogate-ILI) was incorporated in coronary heart disease states and coronary heart events.

The study model shown in Figure 6 demonstrates the mutually exclusive health states when CHD patients start influenza vaccination either with Angina or CA/MI state. The model includes three CHD states which are symbolized in the Solid-line ovals. State numbers 1, 3, and 5 represent History of angina, History of

Figure 7 Health states in Markov model



CA/MI, and Death, respectively, where individuals end up at the end of each cycle (year); these are the definite states programmed in the model. The diamonds and arrows express what happens to the individual within the course of each year as they move between states (thus the shading for "Within Year Events"). These events are incorporated within the model's transition probabilities. Sub-states (dotted-line ovals) were also constructed to represent the different influenza infection incidence of the two alternative modalities, vaccination and no vaccination. When Angina patients (State 1) had CA/MI (Event 2) and moved to History of CA/MI (State 3), they cannot move back to Angina state because myocardial pathology was already developed which was irreversible.

Angina (State 1) and History of CA/MI (State 3) patients may either stay on the same state (dotted-line arrow – P1,1 and P3,3) if no CHD event occurred or die from non-CHD event causes (P1,5 and P3,5), respectively.

Patients who experienced CA/MI event (Event 2 and Event 4) may either die with probabilities of P2,5 and P4,5 or survive with probabilities P2,3 and P4,3), respectively.

The transition between each state and event is determined by probabilities and adjusted factors obtaining from randomized control trials and published systematic reviews.

Because influenza vaccination is recommended annually and we evaluated lifelong vaccination; therefore, the model used 1-year cycle length for full health state. The model starts with patients aged 35 where the evidence of coronary heart disease is firstly identified and the model runs for 45 cycles until the patients age 80 which is the age with the highest incidence of coronary heart disease.[75]

Determine Incremental cost effectiveness ratio (ICER)

The incremental cost effectiveness ratio (ICER) will be computed using incremental cost and incremental effectiveness (QALY) of influenza vaccination comparing to no vaccination strategies defined in the a mathematical statements as follows:

$$ICER_{vacCHD} = (C_{vacCHD} - C_{novac})/(QALY_{vacCHD} - QALY_{novac})$$

$$ICER_{vacAg} = (C_{vacAg} - C_{novac})/(QALY_{vacAg} - QALY_{novac})$$

$$ICER_{vacCA/MI} = (C_{vacCA/MI} - C_{novac})/(QALY_{vacCA/MI} - QALY_{novac})$$

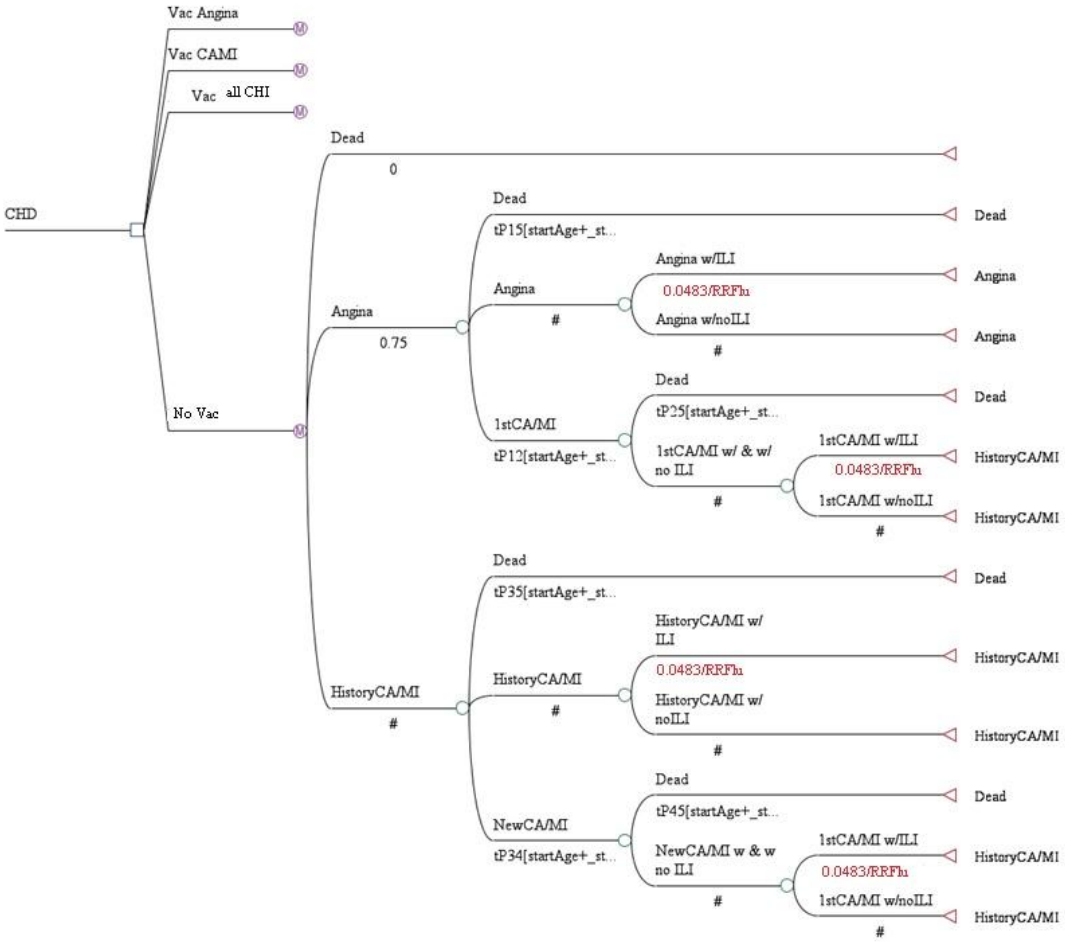
C = cost

Influenza vaccination strategies studies in this study are 1) no influenza vaccination (novac), 2) influenza vaccination to Angina patients only (vacAg) i.e. Angina patients plus patients with history of CA/MI), 3) influenza vaccination to patients with history of CA/MI (vacCA/MI), and 4) influenza vaccination to CHD combined group (vacCHD), as elaborated in decision tree below:

1.1 No influenza vaccination

Patients who do not receive influenza vaccine will have the probability of CHD transition as of normal population. Probability of influenza infection is drawn from influenza vaccine clinical study (placebo arm). Decision tree of no influenza vaccination is depicted in Figure 8.

Figure 8 Decision tree of no influenza vaccination

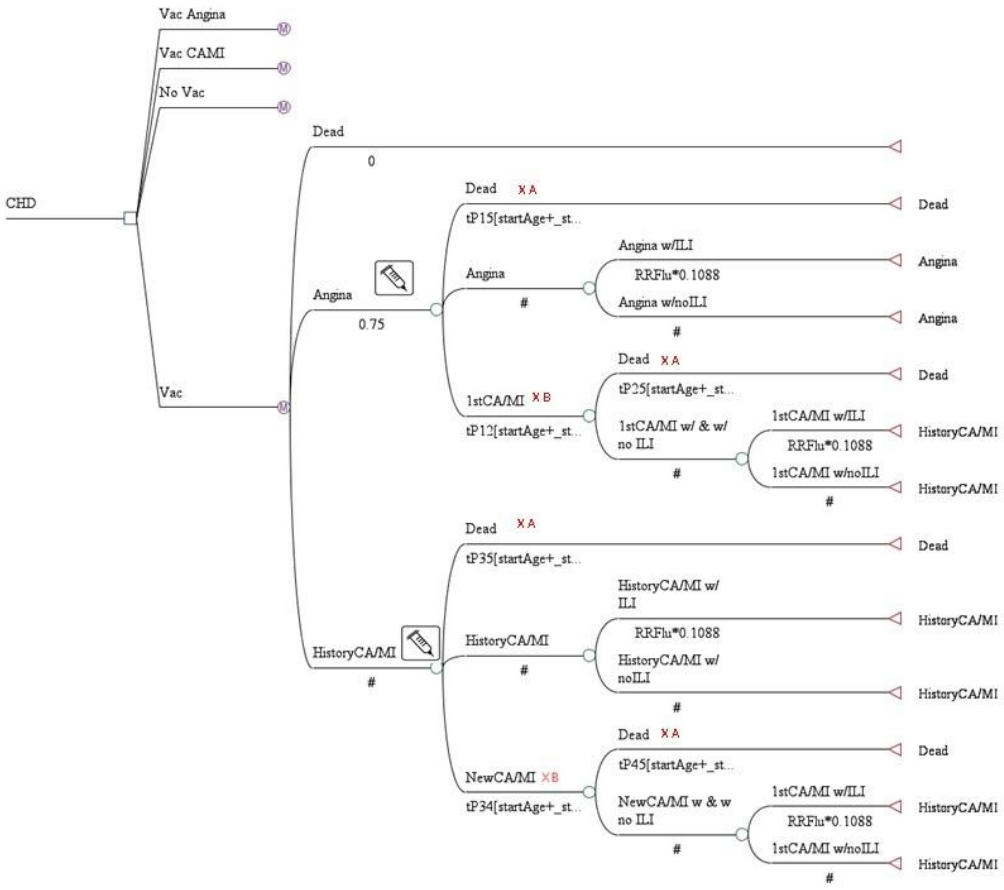


1.2 Influenza vaccination to CHD combined group

CHD combined patients (Angina plus CA/MI) who received influenza vaccine would have the probabilities of CHD transition less than normal population. Decision tree of influenza vaccination in CHD combined patients was depicted in Figure 9. Probability of influenza infection was drawn from the vaccination arm of the

influenza vaccine clinical study in Thailand. The CHD transition probabilities of normal population were adjusted by the risk ratio of acute coronary heart syndrome and coronary death in influenza vaccination comparing to placebo, shown as xA and xB, respectively in the Figure 9-11.

Figure 9 Decision tree of influenza vaccination in CHD combined group

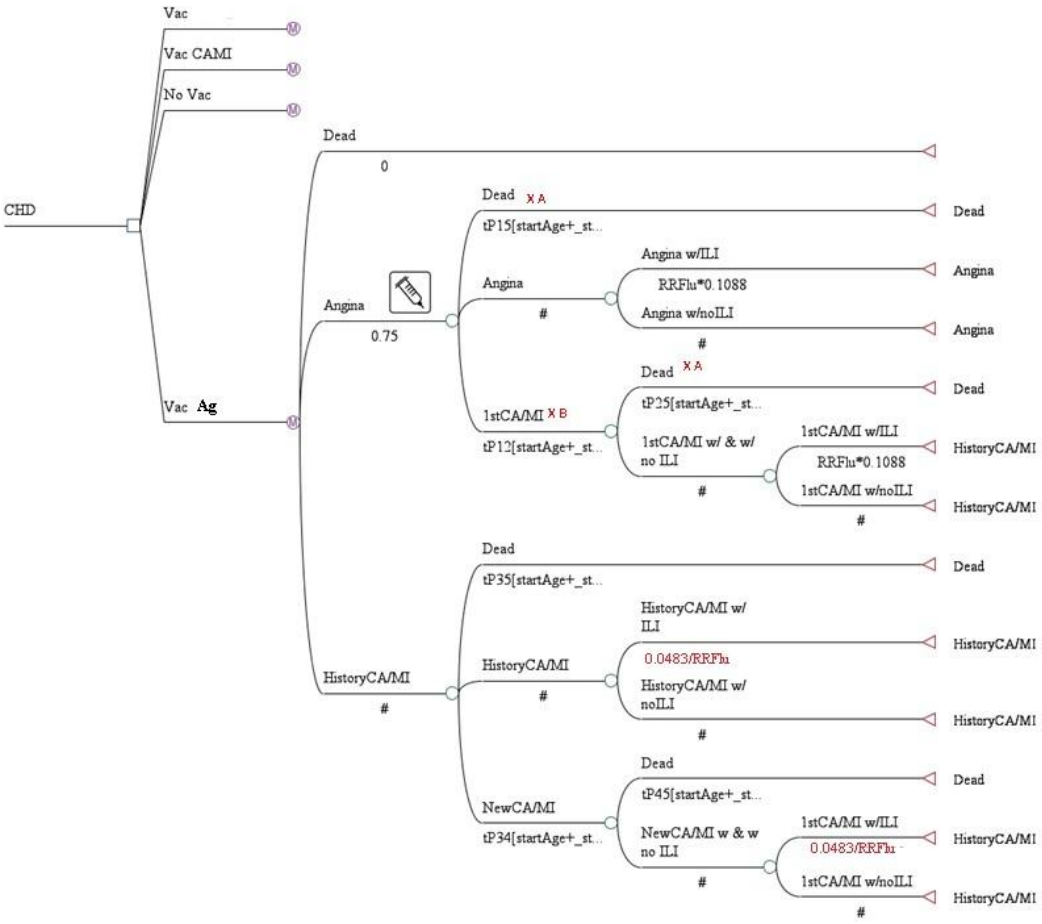


1.3 Influenza vaccination in Angina patients

This vaccination strategy provides influenza vaccine only to Angina patients. Therefore only probabilities of disease transition from Angina stage were adjusted by risk ratio of influenza vaccination. Influenza vaccine was not provided to patients after the first CA/MI was developed; therefore, probabilities of CHD transition afterward are the same as patients who have not received influenza vaccine. Probability of influenza infection of Angina patient was drawn from influenza vaccine study in Thailand (vaccine arm) while influenza infection of CA/MI patient was

drawn from placebo arm. Decision tree of this vaccination strategy was depicted in Figure 10.

Figure 10 Decision tree of influenza vaccination in Angina patients

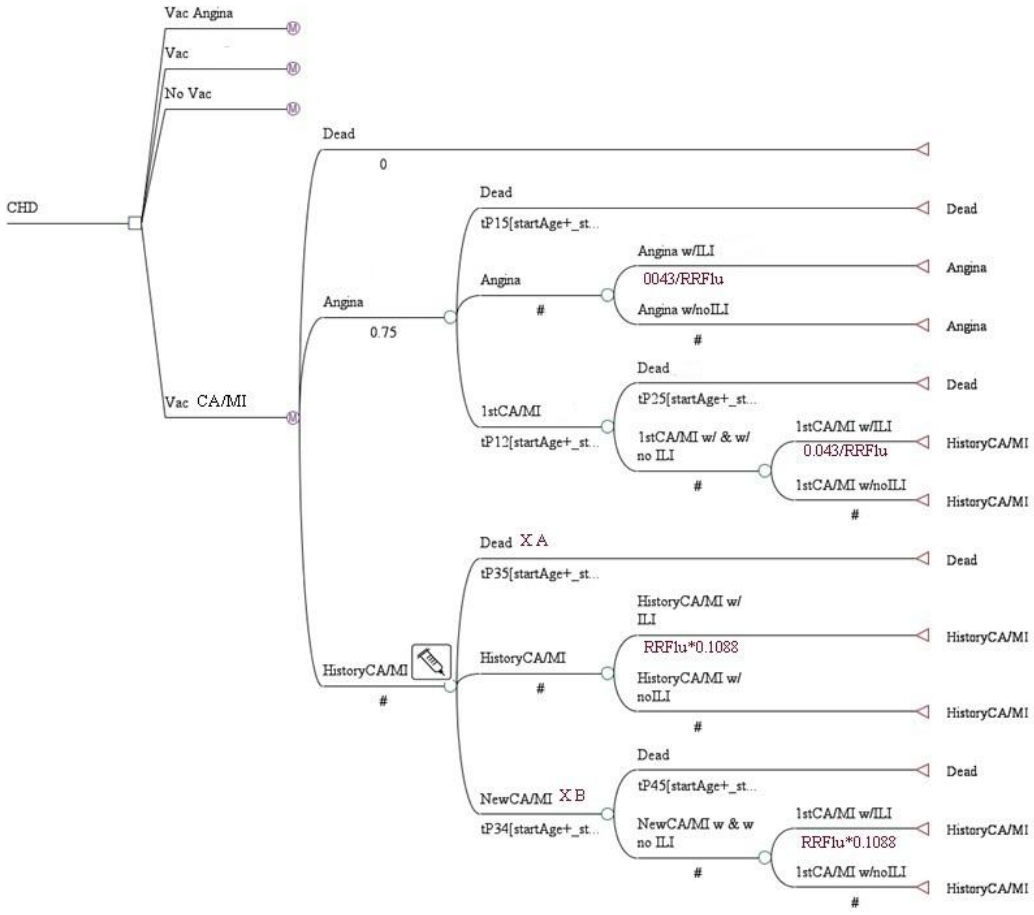


1.4 Influenza vaccination in patients with history of CA/MI

This vaccination strategy provides influenza vaccine only to patients with history of CA/MI. Therefore only probabilities of CHD transition from patient with history of CA/MI stage were adjusted by the result of influenza vaccination clinical study. Influenza vaccine was not provided to Angina patients; therefore, probabilities of CHD transition from Angina patients are the same as patients who have not received influenza vaccination. Probability of influenza infection of patient with history or CA/MI was drawn from influenza vaccine study in Thailand (vaccine arm)

while influenza infection of Angina patient was drawn from placebo arm. Decision tree of this vaccination strategy was depicted in Figure 11.

Figure 11 Decision tree of influenza vaccination in patients with history of CA/MI



The study adopted a societal perspective. The analysis results were showed in the terms of incremental cost, incremental Quality Adjusted Life Years (QALYs), LYG, and ICER in Thai Baht per QALY gained and LYG.

It was assumed that patients remained in the same alternative modality and did not move from vaccination to non-vaccination and vice versa. Markov model was used to compute the lifelong costs and effectiveness of influenza vaccination alternatives in coronary heart diseases patients commencing vaccination with either Angina, CA/MI condition or both conditions.

2. Cost Model

This study applied societal perspective; therefore, costs of the study are composed of:

2.1 Direct medical cost: cost incurred from the disease, its treatment, and prevention (influenza vaccination).

2.1.1 CHD treatment cost: costs were derived from study conducted at Ramathibodi Hospital by Anukoolsawat et al.[76]

330 medical records were retrospectively reviewed from Thai Acute coronary syndrome (ACS) registry. Every consecutive patient hospitalized in Ramathibodi Hospital between August 2002 and December 2003. The direct healthcare costs, indirect healthcare costs incurred by hospitalization, hospital follow-up and mortality from the first hospitalization to the last follow-up. In addition, telephonic checks were done to collect patient's status and to assemble study data. The cost accounting method was used to estimate direct healthcare costs. The costs composed of IPD service, OPD service, IPD Pharmacy, OPD Pharmacy, Investigation, Catherization, Pacemaker & automatic implantable cardioverter-defibrillator (AICD), and CABG. As our study is a yearly analysis for lifetime, we retrieved and classified data in 2 categories

a) ACS costs during the first year:

- The median direct healthcare costs of acute coronary syndrome were 120,298 Baht per patient
- Cost was already adjusted to 2005, Consumer Price Index (CPI) 2005 = 98.5. CPI 2010 = 101.1.
- Cost adjusted to 2010 = 120,298 x 101.1 / 98.5 = 123,473 THB). This study applied societal perspective; therefore, costs of medication and hospital admission

paid by households at 990 Baht, adjusted to 2010 cost = 1,016 THB) were also included.

b) ACS costs for the following year: Anukoolsawat et al.[76] reported second year median direct healthcare costs of acute coronary syndrome and costs of medication and hospital admission paid by households at 12,912 (adjusted to 2010 cost = 12,912 x 101.1/98.5 = 13,253) and 12,810 THB (adjusted to 2010 cost = 12,810 x 101.1 / 98.5 = 13,148 THB), respectively. Since CA/MI is a chronic disease requiring long-term and preventive medication to control disease at a stable condition, it was assumed that the costs of second year from Anukoolsawat et al.[76] study were also applied for the ACS costs for the subsequent years.

Costs were reported at 2005 cost; therefore, CPI 2010 per CPI 2005 (Medical care 101.1/98.5) was used to adjust the study cost data into 2010 cost data.

2.1.2 Influenza treatment cost: costs were obtained from Thai study by Simmerman et al.[77]

A prospective, population-based surveillance system, study was conducted in Thailand to examine cost of influenza management in influenza rapid test positive patients between 2003-2004. Costs of this study reported in US$ which 1 US$ was estimated as 39 THB. Influenza-associated pneumonia hospitalization and outpatient influenza infection were 12,575-75,801 (mid-range: 44,188) cases and 924,478 visits, respectively so the total cases/visits were 968,666 cases/visits. The total direct medical costs were 10.2-27.1 million US$ (mid-range: 18.65 million US$, 727.35 million THB). The estimated cost per case/visit was 750.88 THB. The study was conducted between 2003-2004; therefore CPI 2010 per average 2003-2004 was used to adjust study cost data to 2010 {[101.1/[(94.6+96.8)/2]}. Cost adjusted to 2010 = 793 THB.

2.1.3 Influenza vaccination cost: Influenza vaccine costs were derived from market survey (price list form pharmaceutical companies) and influenza vaccine administration cost was derived from the standard cost lists for health technology assessment prepared by Riewpaiboon.[78]

a) Cost of influenza vaccine

For this study Fluveris (GSK) and Influvac (Abbott) were used as a representative for vaccine cost calculation as they are inactivated influenza vaccines which are recommended for patients with risk. Pharmaceutical industry's average retail price (30 September 2011 – VAT included) of those 2 vaccines are:

- Fluveris: price list = 318.86 THB
- Influvac: price list = 321.00 THB

Average price = 319.93 THB

b) Cost of vaccine administration and logistic: Vaccination cost and vaccine logistic cost were derived from standard cost lists for health technology assessment by Riewpaiboon.[78]

- Vaccine administration cost = 115.12 THB
- Vaccine logistic cost (4.92%) = 15.74 THB

Total cost of influenza vaccine = 130.86 THB (2009 cost)

Adjusted to year 2010; CPI 2010/CPI 2009 = 101.1/100.9

Vaccine administration and logistic cost (2010) = 131.12 THB

Total cost of vaccine, administration, and logistic cost = 451.05 THB

2.2 Direct non-medical cost: Direct non-medical costs i.e. caregiver time and transportation were derived from study conducted at Ramathibodi Hospital by Anukoolsawat et al.[76] for ACS and study conducted in Thailand by Simmerman et al.[77] for influenza.

2.2.1 ACS: A prospective interviews (either face to face or telephone) of 193 Thai ACS registry patients and their relatives who came to the out-patient department for follow-up during the study period (2005) to cover 1-33 months

after being diagnosed as ACS. The monthly median cost throughout the first year was 3,215 THB (adjusted 2010 cost = 3,300 THB) and cost for the second year was 4,650 THB (adjusted 2010 cost = 4,773 THB).[76]

Costs were incurred in 2005; therefore, 2010 per 2005 consumer price index (Medical care 101.1/98.5) was used to adjust the study cost data into 2010 cost data.

2.2.2 Influenza:[77]

- Travelling cost to healthcare facility for influenza treatment = 1.6-2.2 (mid-range = 1.9) million US$.
- This study applied 39 THB per 1 $ so the total cost = 1.9 x 39 = 74.1 million THB.
- Number of OPD patients = 924,478 cases, so the cost/patient = 74.1 x 1,000,000 / 924,478 = 80.15 THB.
- Cost was incurred between 2003-2004 so average 2003 CPI and 2004 CPI was used for 2010 cost adjustment. CPI 2003 = 94.6 and CPI 2004 = 96.8 so average CPI 2003-2004 = 95.7, CPI 2010 = 101.1
- The travelling cost adjusted to 2010 = 80.15 x 101.1 /96.8 = 85 THB / patient
- Travelling cost to healthcare facility for influenza vaccination was not included as it is assumed that vaccination was provided during the routine follow-up visit at cardiovascular clinic.

2.3 Indirect cost: Costs incurred from opportunity loss due to illness, hospitalization, informal care, and death were be derived from study conducted at Ramathibodi Hospital by Anukoolsawat et al.[76] for ACS. For influenza, indirect costs were obtained from Thai study by Simmerman et al.[77] The opportunity loss for

vaccination will not be included as it is assumed that vaccination is provided during the routine follow-up visit at cardiovascular clinic.

1.3.1 ACS:[76]

a) Prospective data collection: Same interview as conducted for direct non healthcare costs was conducted to obtain indirect healthcare costs. The median cost of productivity lost incurred from monthly morbidity, excluding hospital admission and follow-up costs during 12 months and the 12-24 months was 26,469 THB (adjusted 2010 cost = 27,168 THB) and 15,157 THB (adjusted 2010 cost = 15,557 THB), respectively. Costs were incurred in 2005; therefore, 2010 per 2005 consumer price index (Medical care 101.1/98.5) was used to adjust the study cost data into 2010 cost data.

b) Retrospectively data collection: Same retrospective review as conducted for direct healthcare costs was conducted to obtain indirect costs incurred by days lost from hospitalization and follow-up. The calculated lost productivity cost was 4,416 THB per patients. Costs were incurred in 2005; therefore, 2010 per 2005 consumer price index (Medical care 101.1/98.5) was used to adjust the study cost data into 2010 cost data.

2.3.2 Influenza:[77] Costs from work absenteeism from outpatient influenza and influenza pneumonia were 11.1-24.9 (mid-range = 18) million US$ and 0.5-8.7 (mid-range = 4.6) million US$. The indirect cost per influenza case/visit was 724.71 THB (adjusted 2010 cost = 933 THB).

Table 1 Cost data inputs for cost utility analysis

Parameter description	Distribution	Mean	SE	Ref
Direct medical cost - adjusted to 2010 (cost/year)				
Median direct health care cost (ACS) - first year	Gamma	123,473*	849.6206	Anukoolsawat et al. 2006[76]
Median direct health care cost (ACS) - subsequent year	Gamma	13,253*	91.1930	
Mid-range treatment cost of influenza (one time cost)	Gamma	793#	0.1007	Simmerman et al. 2006[77]
Cost of influenza vaccine,	Gamma	451	1.5662	Market survey
Cost of influenza vaccine administration and logistic				Riewpaiboon 2009[78]
Median cost of medication and hospitalization (ACS) paid by household (first year)	Gamma	1,016*	9.1428	Anukoolsawat et al. 2006[76]
Median cost of medication and hospitalization (ACS) paid by household (subsequent year)	Gamma	13,148*	118.3029	

** Median cost was used as mean for SE calculation*

 # Mid-range was used as mean for SE calculation

Table 1 Cost data inputs for cost utility analysis (Continue)

Parameter description	Distribution	Mean	SE	Ref
Direct non-medical cost - adjusted to 2010 (cost/year)				
Median direct non-healthcare cost (ACS) - first year	Gamma	3,300*	29.6924	Anukoolsawat et al. 2006[76]
Median direct non-healthcare cost (ACS) - subsequent year	Gamma	4,772*	42.9437	
Transportation cost (influenza)	Gamma	85	0.0108	Simmerman et al. 2006[77]
Indirect cost Opportunity lost due to disease or death- adjusted to 2010 (cost/year)				
Median indirect cost due to morbidity exclude hospitalization (ACS) - first year	Gamma	27,168*	244.4494	Anukoolsawat et al. 2006[76]
Median indirect cost due to ACS admission and FU - first year	Gamma	4,532*	40.7776	
Median indirect cost due to morbidity exclude hospitalization (ACS) - subsequent year	Gamma	15,557	139.9779	
Cost of work absenteeism due to outpatient influenza	Gamma	933	0.1213	Simmerman et al. 2006[77]
Probability of CHD Progression				Hoerger et al. 2004[63]

3. Disease Transition Probabilities

The disease transition probabilities composes of 3 elements; CHD transition probabilities; adjusting factors of CHD transition probabilities to account for the decreased risk of CHD in patient received influenza vaccine (Relative risk of CHD); and probability of influenza infection in 2 scenarios, with influenza vaccine and without influenza vaccine.

3.1 CHD progression

The data used for the estimation of probabilities of CHD progression were drawn from 2 studies, Weinstein et al. 1987[62] and Hunink et al. 1997.[64] It was assumed that patients enrolled into those studies were not received influenza vaccine as it could not be confirmed if patient enrolled into the studies received influenza vaccination. There are 10 CHD progression probabilities demonstrated as follows:

3.1.1 Probability that Angina patients can experience the 1st CA/MI event - P1,2 (t) (Angina → 1st CA/MI)

P1,2 composes of 2 values, probability that 1st CA/MI will be occurred in Angina patient – P(CA/MI / Angina) and Age relative risk (AgeRisk). Therefore P1,2 would be calculated from the equation below: P1,2 = P(CA/MI / Angina) x AgeRisk

P(CA/MI / Angina) = 0.0303 for males, 0.0123 for females

Age relative risk shown in Table 2

Table 2 Relative Risk of Cardiac Arrest or Myocardial Infarction Given a History of Angina (AgeRisk1)

Age (years)	Relative Risk
35-44	0.261
45-54	0.630
55-64	1.000
65-74	1.371
75+	1.826

Source: Hunink et al. 1997[64]

3.1.2 Probability that Angina patients may die from angina-related causes - P1,5 (t) (Angina → Death)

P1,5 (t) = P(Death / History of Angina)

See Table 3

Table 3 Probability of Death Given a History of Angina

Age (years)	Probability (Death / History of Angina	
	Male	Female
35-44	0.00460	0.00249
45-54	0.01070	0.00618
55-64	0.01841	0.01196
65-74	0.03267	0.02507
75+	0.10591	0.09638

Source: Weinstein et al. 1987[62]

3.1.3 Probability that Angina patients may continue with angina - P1,1 (t) (Angina → Angina)

There are 3 probabilities going out from Angina state and all of them would be added to 1. So the P1,1 was calculated as shown in the equation below:

P1,1 (t) = 1 – P1,2 (t) – P1,5 (t)

3.1.4 Probability of death after the 1st CA/MI event - P2,5 (t) (1st CA/MI → Death)

P2,5 (t) = P(Death / 1st CA/MI)

P2,5 composes of 2 parts, 1) probability of death from CA – P(death/CA) and 2) probability of death form 1st CA/MI – P(death from CA/MI). P2,5 was calculated as shown in the equation below:

$$= P(\text{Death} / \text{CA}) * P(\text{CA} / \text{CA/MI}) + P(\text{Death} / 1^{st}\ \text{MI}) * P(\text{MI} / \text{CA/MI})$$

P(CA / CA/MI) = 0.2 (probability of CA occurrence in both CA and MI patients)

P(MI / CA/MI) = 0.8 (probability of MI occurrence in both CA and MI patients)

P(Death / CA) = 1 – [P(Survival to Admission) * P(Survival to Discharge)]

See Table 4 and 5

Table 4 Probability of Death Given Cardiac Arrest

Age (yrs)	Probability		
	Survival to Hospital Admission	Survival to Discharge	Death Given CA
35-44	0.3885	0.6446	0.7496
45-54	0.3316	0.5837	0.8064
55-64	0.2747	0.4974	0.8634
65-75	0.2178	0.3661	0.9203
75+	0.1609	0.1419	0.9772

Source: Hunink et al. 1997[64]

Table 5 Probability of death after 1st Myocardial Infarction

Age (years)	Probability (Death / 1st MI)	
	Male	Female
35-44	0.0154	0.0154
45-54	0.0336	0.0336
55-64	0.0730	0.0730
65-75	0.1587	0.1587
75+	0.2953	0.2953

Source: Hunink et al (1997) [64]

3.1.5 Probability of survive after the 1st CA/MI event- P2,3 (t) (1st CA/MI → History of CA/MI)

$$P2,3\ (t) = 1 - P2,5\ (t)$$

3.1.6 Probability that patients with a history of CA/MI may experience a new CA/MI event - P3,4 (History of CA/MI → New CA/MI)

$$P3,4 = P(CA/MI \ / \ History\ of\ CA/MI) * AgeRisk1$$

$$= [P(CA \ / \ History\ of\ CA/MI) + P(MI \ / \ History\ of\ CA/MI)] * AgeRisk1$$

P(CA / History of CA/MI) = 0.01432 for males, 0.01132 for females

P(MI / History of CA/MI) = 0.0573 for males, 0.0453 for females

Source: Hoerger et al. (1997)[63]

3.1.7 Probability that patient may die from chronic conditions related to MI - P3,5 (t) (History of CA/MI → Death)

$$P3,5\ (t) = P(MI\ Chronic\ Death)$$

See Table 6

As CA event leads to high probability of death; therefore, probability that patient may die from chronic conditions related to CA was disregarded.

Table 6 Probability of Death from Chronic Myocardial Infarction

Age (years)	Probability (MI Chronic Death)	
	Male	Female
35-44	0.00460	0.00249
45-54	0.01070	0.00618
55-64	0.01841	0.01196
65-75	0.03267	0.02507
75+	0.10591	0.09638

Source: Weinstein et al. 1987[62]

3.1.8 Probability that patients with a history of CA/MI survive with no additional CHD event - P3,3 (t) (History of CA/MI → History of CA/MI)

$$P3,3\ (t) = 1 - P3,5\ (t) - P3,4\ (t)$$

3.1.9 Probability of death after experience a new CA/MI - P4,5 (t)

(New CA/MI → Death)

$$P4,5\ (t) = P(CA\ /\ CA/MI) * P(Death\ /\ CA) + P(MI\ /\ CA/MI) * P(Death\ /\ Recurrent\ MI)$$

$$P(CA\ /\ CA/MI) = 0.2$$

$$P(MI\ /\ CA/MI) = 0.8$$

$$P(Death\ /\ CA) = 1 - [P(Survival\ to\ Admission) * P(Survival\ to\ Discharge)]$$

See Table 4 for probability of Death Given Cardiac Arrest

See Table 7 for probability of death given recurrent MI

Table 7 Death Rates After recurrent Myocardial Infarction

Age (years)	Probability (Death / Recurrent MI)	
	Male	Female
35-44	0.0867	0.0867
45-54	0.1120	0.1120
55-64	0.1446	0.1446
65-75	0.1867	0.1867
75+	0.2953	0.2953

Source: Hoerger et al. 2004[63]

3.1.10 Probability of survival after experience a new CA/MI - P4,3 (t)

(New CA/MI → History of CA/MI)

$P_{4,3}(t) = 1 - P_{4,5}(t)$

All probabilities of CHD transition are demonstrated in Table 8 in the next page.

Table 8 The probabilities of CHD transition in normal population (assume with no infleunza vaccination)

Age Range	35-44			45-54			55-64			65-74			75+		
CHD Transition Probability	M	F	Weighted average*	M	F	Weighted average*	M	F	Weighted average*	M	F	Weighted average*	M	F	Weighted average*
Probability of Death Given a History of Angina (P1,5)	0.00460	0.00249	0.00347	0.01070	0.00618	0.00827	0.01841	0.01196	0.01494	0.03267	0.02507	0.02858	0.10591	0.09638	0.10079
Relative Risk of Cardiac Arrest or Myocardial Infarction Given a History Angina (AgeRisk1)	0.26100			0.63000			1.00000			1.37100			1.82600		
Probability of 1st CA/MI Given a history of Angina (P1,2)	0.00791	0.00313	0.00534	0.01909	0.00756	0.01289	0.03030	0.01200	0.02046	0.04154	0.01645	0.02805	0.05533	0.02191	0.03736
Probability of staying in history of Angina state (P1,1)	0.98749	0.99438	0.99119	0.97021	0.98626	0.97884	0.95129	0.97604	0.96460	0.92579	0.95848	0.94337	0.83876	0.88171	0.86185
Probability of Death Given CA	0.74960			0.80640			0.86340			0.92030			0.97720		
Probability of Death Given the 1st MI	0.01540			0.03360			0.07300			0.15870			0.29530		
Probability of CA from CA/MI	0.2														
Probability of MI from CA/MI	0.80000														
Probability of Death from 1st CA/MI (P2,5)	0.16224			0.18816			0.23108			0.31102			0.43168		
Probability of survive from 1st CA/MI (P2,3)	0.83776			0.81184			0.76892			0.68898			0.56832		
Probability of CA Given a History of CA/MI	0.01432	0.01132	0.01271												

Weighted average by gender used male : female ratio = 9.2 : 10.7 (Source: Tatsanavivat et al. 1998)[79]

Table 8 The probabilities of CHD transition in normal population (assume with no infleunza vaccination) (Continue)

	35-44			45-54			55-64			65-74			75+		
	M	F	Weighted average*	M	F	Weighted average*	M	F	Weighted average*	M	F	Weighted average*	M	F	Weighted average*
Probability of MI Given a History of CA/MI	0.05730	0.04530	0.05085												
Probability of new CA/MI Given a history of CA/MI (P3,4)	0.01869	0.01478	0.01659	0.04512	0.03567	0.04004	0.07162	0.05662	0.06355	0.09819	0.07763	0.08713	0.13078	0.10339	0.11605
Probability of Death Given a History of CA/MI (P3,5) -assume to be equal to Death from chronic MI	0.00460	0.00249	0.00347	0.01070	0.00618	0.00827	0.01841	0.01196	0.01494	0.03267	0.02507	0.02858	0.10591	0.09638	0.10079
Probability of staying in history of CA/MI state (P3,3)	0.97671	0.98273	0.97995	0.94418	0.95815	0.95169	0.90997	0.93142	0.92150	0.86914	0.89730	0.88428	0.76331	0.80023	0.78316
Probability of Death from recurrent MI	0.08670			0.11200			0.14460			0.18670			0.29530		
Probability of Death from recurrent CA/MI (P4,5)	0.21928			0.25088			0.28836			0.33342			0.43168		
Probability of survive from recurrent CA/MI (P4,3)	0.78072			0.74912			0.71164			0.66658			0.56832		

Weighted average by gender used male : female ratio = 9.2 : 10.7 (Source: Tatsanavivat et al. 1998)[79]

3.2 Disease Risk Reduction

The risk of CHD and influenza events were reduced by influenza vaccine. Therefore risk ratios of CHD achieved by influenza vaccine from systematic analysisby Keller et al.[25] and relative risk of influenza from study conducted by Rungnirand et al.[80] were applied to the CHD transition probabilities and influenza probablities, respectively as follows:

3.2.1 Risk ratio of cardiovvascular death, 0.39, was multiplied to P1,5; P2,5; P3,5; and P4,5 to account for the decreased risk of cardiovascular death among CHD patient received influenza vaccine, 95% CI 0.02 to 0.77 was used for PSA and was also transformed to SD/SE for PSA.

3.2.1 Risk ratio of Acute myocardial infarction (AMI), 0.85, was multiplied to P1,2 and P3,4 to account for the decreased risk of AMI among patient received influenza vaccine, 95% CI 0.44 to 1.62 was used for DSA and was also transformed to SD/SE for PSA.

3.2.2 Relative risk of influenza related to influenza infection, 0.44 (relative risk, 95% CI and SD were calculated from study results as shown in Appendix B)

Risk ratios and relative risk were shown in Table 9

Table 9 Risk ratios and relative risk achieved by influenza vaccination

Parameter description	Distribution	Mean	SE	Ref
Risk Ratio of death in influenza vaccination compared to no vaccination group (A)	Log normal	0.39	0.3439	Keller et al. 2008[25]
Risk Ratio of AMI in influenza vaccination compared to no vaccination group (B)	Log normal	0.85	0.3325	
Relative Risk of ILI in influenza vaccination (RRflu)	Log normal	0.44	0.3278	Rungnirand et al. 2005[80]
Probability of ILI in influenza vaccination group	Beta	0.0483		
Probability of ILI in no influenza vaccination group	Beta	0.1088		

4. Utility

This study evaluated effectiveness of influenza vaccination in CHD and influenza aspects; therefore, there are 2 features of utility involved in this analysis, utility in CHD patients and influenza patients.

4.1 The utility scores of patients with existing CHD at different disease severity (Angina and CA/MI) during the first year and subsequent year were derived from studies conducted by Nease et al.[8] and Tsevat et al.[61]

4.2 The utility loss due to influenza infection compared to healthy was obtained from study conducted by Velasco et al.[81]

Details of utility were shown in Table 10 below:

Table 10 Utilities in CHD and influenza

Parameter description	Distribution	Mean	SE	Ref
Utility in CA/MI patient - 1st year	Beta	0.87	0.0255	Tsevat et al. 1994[61]
Utility in Angina patient	Beta	0.997	0.0008	Nease et al. 1995[8]
Utility in CA/MI patient - subsequent year	Beta	0.91	0.0255	Tsevat et al. 1994[61]
Utility in influenza patient	Beta	0.294	0.0608	Velasco et al. 2009[81]
Utility in healthy (compared to influenza)	Beta	0.941	0.0170	

5. Cost-Effectiveness Analysis

Analyses of this study were performed using TreeAge Pro 2011 statistical software following the steps as shown below:

5.1. Construct decision analytic model

5.2 Define the Markov at the chance node(s)

5.3 Label and annotate CHD transition probabilities and Markov components at decision/ chance node(s) and branch(s) of the model (discounting 3%, 45 cycles)

5.4 Enter probability expressions

5.5 Define variable name and definition then enter its value, repeat this for all variables

5.6 Perform Cost-Effectiveness Analyses and Rankings then generate the report(s), graph(s)

5.7 Add variables' low value and high value for deterministic sensitivity analysis

5.8 Perform one-way sensitivity analysis, Tornado Diagram then generate graph and report

5.9 Add variables' distribution for probabilistic sensitivity analysis

5.10 Perform Monte Carlo Simulation, Sampling (Probabilistic Sensitivity), define number of samples

5.11 Generate report(s) and graph(s) (Cost-effectiveness analysis, Ranking, Incremental CE Scatterplots, CE acceptability Curve, and Monte Carlo Strategy Selection at defined WTP)

6. Uncertainty analysis

6.1 Univariate Sensitivity Analyses were performed in individual input variable to investigate the influence on Net Benefit of influenza vaccination strategy. 95% confidence intervals (directly obtained from or extracted from clinical study and then convert to desirable form – see Appendix A) of all data inputs were used to estimate possible range of low value and high value.

6.2 Probabilistic Sensitivity Analysis (PSA) was performed by Monte Carlo simulation. It was carried out using TreeAge Pro 2011. Monte Carlo simulation was used by involving random sampling of each variable under the specified probability distribution of each input parameter which was assigned based to their feature to

indicate the feasible value range in which each input variable could achieve. Beta distribution was chose for the probability and utility variables, Gamma distribution was used for all cost parameters and Log normal was used for Relative Risk.

The simulation obtained one value from each variable distribution simultaneously to compute cost and effectiveness pairs. A Monte Carlo simulation was recurred 10,000 times to deliver a possible value range of the specified probability distribution, each time using different randomly all selected values. The results were presented as costs, effectiveness (QALYs) and ICER in the Research Result chapter.

CHAPTER IV

RESEARCH RESULT

This is a lifetime cost utility analysis of influenza vaccination for reducing coronary heart disease (CHD) progression and influenza event(s) when provide influenza vaccination to CHD patients at different disease severities. The following three sets of input parameters are required; 1) utility scores of CHD patients at different disease severities during the first year and the following years and utility scores lost due to influenza infection, 2) probabilities of CHD transition and probability of influenza occurance, 3) costs. This chapter provides values and features of each input parameter categorized by group as described in the first section. Input parameters were entered into the Markov model and computed as described in chapter III. The cost utility analyses are reported in term of incremental cost per QALY gained and Life Year gained (LYG) of 3 influenza vaccination strategies, in CHD combined group, in Angina patients, and in patients with history of CA/MI in comparison with no influenza vaccination. Details of analysis inputs and outputs from computer software are included in Appendix D. The last section composes of 2 sets of sensitivity analyses, deterministic and probabilistic.

1. Model input parameters

1.1 Utility scores of Angina patient, patient with history of CA/MI (define in this study as Utility in CA/MI patient - subsequent year), patient with ongoing CA/MI (define in this study as Utility in CA/MI patient - first year) and utility scores lost due to influenza infection (define in this study as Utility in healthy minus Utility in influenza patient).

1.2 Probabilities of CHD transition and probability of infleunza occurance.

1.3 The Disease Risk Reduction for probabilities of CHD transition and influenza events achieved by influenza vaccination.

1.4 Direct medical cost, direct non-medical cost, indirect cost of acute coronary syndrome and influenza .

All model input parameters are shown in Table 11.

Table 11 Mean and SE of transitional probability parameters and input parameters

Parameter description	Distribution	Mean	SE	Ref
Risk Ratio of death in influenza vaccination compared to no vaccination group	Log normal	0.39	0.3439	Keller et al. 2008[25]
Risk Ratio of AMI in influenza vaccination compared to no vaccination group	Log normal	0.85	0.3325	
Relative Risk of ILI in influenza vaccination	Log normal	0.44	0.3278	Rungnirand et al. 2005[80]
Probability of ILI in influenza vaccination group	Beta	0.0483		
Probability of ILI in no influenza vaccination group	Beta	0.1088		
Utility				
Utility in CA/MI patient - first year	Beta	0.87	0.0255	Tsevat et al. 1994[61]
Utility in Angina patient	Beta	0.997	0.0008	Nease et al. 1995[8]
Utility in CA/MI patient - subsequent year	Beta	0.91	0.0255	Tsevat et al. 1994[61]
Utility in influenza patient	Beta	0.294	0.0608	Velasco et al. 2009[81]
Utility in healthy (compared to influenza)	Beta	0.941	0.0170	

Table 11 Mean and SE of transitional probability parameters and input parameters (Continue)

Parameter description	Distribution	Mean	SE	Ref
Direct medical cost - adjusted to 2010 (cost/year)				
Median direct health care cost (ACS) - first year	Gamma	123,473*	849.6206	Anukoolsawat et al. 2006[76]
Median direct health care cost (ACS) - subsequent year	Gamma	13,252*	91.1930	
Mid-range treatment cost of influenza (one time cost)	Gamma	793#	0.1007	Simmerman et al. 2006[77]
Cost of influenza vaccine,	Gamma	451	1.5662	Market survey
Cost of influenza vaccine administration and logistic				Riewpaiboon 2009[78]
Median cost of medication and hospitalization (ACS) paid by household (first year)	Gamma	1,016*	9.1428	Anukoolsawat et al. 2006[76]
Median cost of medication and hospitalization (ACS) paid by household (subsequent year)	Gamma	13,148*	118.3029	
Direct non-medical cost - adjusted to 2010 (cost/year)				
Median direct non-healthcare cost (ACS) - first year	Gamma	3,300*	29.6924	Anukoolsawat et al. 2006[76]
Median direct non-healthcare cost (ACS) - subsequent year	Gamma	4,772*	42.9437	
Transportation cost (influenza)	Gamma	85	0.0108	Simmerman et al. 2006[77]

** Median cost was used as mean for SE calculation*

 # Mid-range was used as mean for SE calculation

Table 11 Mean and SE of transitional probability parameters and input parameters (continue)

Parameter description	Distribution	Mean	SE	Ref
Indirect cost Opportunity lost due to disease or death- adjusted to 2010 (cost/year)				
Median indirect cost due to morbidity exclude hospitalization (ACS) - first year	Gamma	27,168*	244.4494	Anukoolsawat et al. 2006[76]
Median indirect cost due to ACS admission and FU - first year	Gamma	4,532*	40.7776	
Median indirect cost due to morbidity exclude hospitalization (ACS) - subsequent year	Gamma	15,557	139.9779	
Cost of work absenteeism due to outpatient influenza	Gamma	933	0.1213	Simmerman et al. 2006[77]

Proportion of Angina patients : patients with history of CA/MI is assumed 0.75 : 0.25 (Source: Pattanaprichakul 2007)[82]

** Median cost was used as mean for SE calculation.*

2. Cost Utility analysis

Based on the societal perspective; costs, QALYs, and incremental cost effectiveness ratio per QALY gained and Life Year gained (LYG) of influenza vaccination strategies in comparison to no vaccination are shown in the Table 12.

Table 12 Cost-effectiveness results obtained from the analysis (Base case)

Calculated all incremental relative to the least costly option (Base case)

Influenza vaccination strategy	Total Cost (THB)	Total effectiveness (QALYs)	Total LYs	Incremental cost (THB)	Incremental effectiveness (QALYs)	LYG	ICER (THB/ QALY gained)	ICER (THB/ LYG)
No Vaccine	346,437	18.26	18.89					
Vaccine in Angina	360,786	19.96	20.60	14,349	1.70	1.71	8,420	8,372
Vaccine in CAMI	437,901	19.72	20.49	91,464	1.46	1.61	62,711	56,984
Vaccine in all CHD	454,664	21.46	22.25	108,227	3.20	3.36	33,813	32,200

Calculated all incremental relative to the least costly option (Base case)

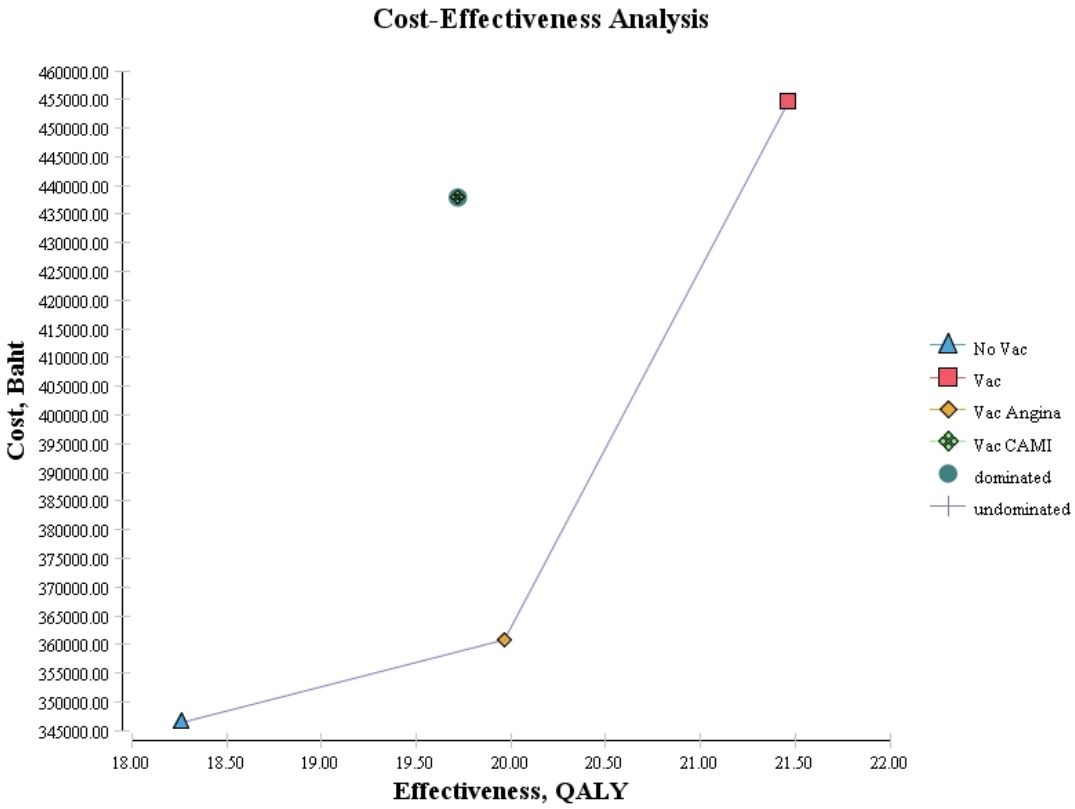
Influenza vaccination strategy	Total Cost (THB)	Total effectiveness (QALYs)	Total LYs	Incremental cost (THB)	Incremental effectiveness (QALYs)	LYG	ICER (THB/ QALY gained)	ICER (THB/ LYG)
No Vaccine	346,437	18.26	18.89					
Vaccine in Angina	360,786	19.96	20.60	14,349	1.70	1.71	8,420	8,372
Vaccine in CAMI	437,901	19.72	20.49	77,115	(0.25)	-0.11	dominated	dominated
Vaccine in all CHD	454,664	21.46	22.25	16,763	1.74	1.76	9,622	9,546

From societal perspective, the incremental costs for influenza vaccination in Angina patients, CA/MI patients, and CHD combined group were 14,349, 91,464, and 108,227 THB, respectively and the QALYs gained were 1.7, 1.46, and 3.2, respectively. The minimum ICER was the ICER of influenza vaccination in Angina patients (ICER: 8,420 THB per QALY gained). The influenza vaccination strategy in Angina patients appears more cost-effectiveness than other strategies. When Life-year gained (LYG) was considered as effectiveness, total ICER per LYG of each influenza vaccination strategy showed similar results and the minimum ICER was also the ICER of influenza vaccination in Angina patients (ICER: 8,372 THB/LYG).

Figure 12 is a Cost-Effectiveness Analysis Graph (Base case) depicting the comparison of all influenza vaccination strategies in this analysis. The graph shows the 4 influenza strategies (including no influenza vaccination) based on cost and effectiveness. As the line between interventions becomes more vertical, the cost-effectiveness ration becomes less favorable because costs are increasing faster than benefits (effectiveness) are. The slope of the line between 2 interventions represents the ICER. A lower ICER denotes more favorable cost-effectiveness. The lines connecting the 3 strategies (no vaccination, vaccination in Angina patients, and vaccination in CA/MI patients) are called cost effectiveness frontier. The influenza vaccination in CA/MI patients with costs and QALYs above and to the left of the cost-effectiveness frontier would be dominated or less cost-effective than vaccination strategies on the frontier and would be rejected.

The cost-effectiveness of influenza vaccination in CHD combined group showed less cost effectiveness but yielded more QALY (more expensive and more effectiveness) and ICER (33,813 THB per QALY gained) was still lower than WTP at 100,000 THB per QALY.

Figure 12 Cost-Effectiveness Analysis of influenza vaccination (Base case)

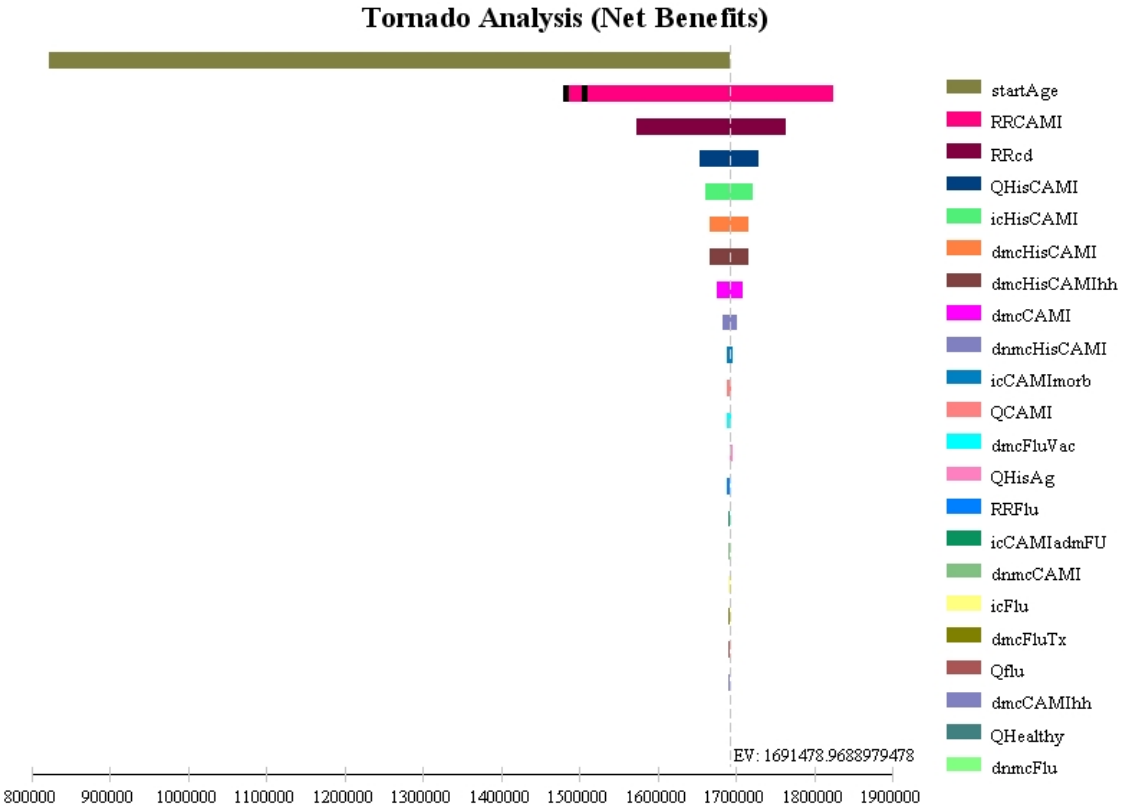


3. Sensitivity analysis

3.1 Univariate Sensitivity Analysis

Tornado diagram was used to display univariate sensitivity analyses. The diagram shows influence of uncertainty of each individual variable demonstrating in each bar on the Net Benefits (NB). Model parameters that greately influenced the NB were started age of influenza vaccination placing on the top of the diagram follows by Relative Risk of CA/MI, Relative Risk of coronary death, and 4 parameters of patient with history of CA/MI (utility, indirect cost, direct medical cost, and direct medical cost paid by household), respectively. Input parameters with the least influence to NB were direct medical cost of influenza, utility in healthy, direct medical cost of patient with CA/MI paid by household, utility of patient with influenza, direct medical cost of influenza treatment, respectively as shown in Figure 13.

Figure 13 Tornado diagram of univariate analyses



3.2 Probabilistic sensitivity analysis (PSA)

The result of the probabilistic model, which by assigning distributions to all parameters allows the parameter uncertianty to be propagated throughlut the model, are presented in Table 13 and Figure 14. The PSA demonstrated similar result of the base case with the same conclusion that vaccination in Angina patients was the most cost-effectiveness and vaccinaiton in CHD combined group was more expensive and more effectiveness.

The 95% CI of the total costs, total effectiveness, and net monetary benefit (NMB) are shown in Table 14. The total costs, total effectiveness, and NMB of the base case falled within 95% CI of Monte Carlo simulation except a little deviation in effectiveness result in the no vaccination (18.26 QALY) which was out of the corresponding PSA 95% CI 5.28 to 18.20.

Table 13 Cost-effectiveness Analysis (Monte Carlo Simulation)

Calculated all incrementals relative to the least costly option: no influenza vaccination (Monte Carlo simulation)

Influenza vaccination strategy	Total Cost (THB)	Total effectiveness (QALYs)	Total LYs	Incremental cost (THB)	Incremental effectiveness (QALYs)	LYG	ICER (THB/QALY gained)	ICER (THB/LYG)
No Vaccine	223,019	10.81	11.09					
Vaccine in Angina	260,660	13.51	13.85	37,641	2.70	2.76	13,942	13,655
Vaccine in CA/MI	349,131	12.68	13.16	126,112	1.88	2.07	67,201	60,941
Vaccine in CHD combined	410,112	15.69	16.26	187,093	4.88	5.17	38,333	36,207

Calculated all incrementals relative to the next least costly option (Monte Carlo simulation)

Influenza vaccination strategy	Total Cost (THB)	Total effectiveness (QALYs)	Total LYs	Incremental cost (THB)	Incremental effectiveness (QALYs)	LYG	ICER (THB/QALY gained)	ICER (THB/LYG)
No Vaccine	223,019	10.81	11.09					
Vaccine in Angina	260,660	13.51	13.85	37,641	2.70	2.76	13,942	13,655
Vaccine in CA/MI	349,131	12.68	13.16	88,471	-0.82	-0.69	dominated	dominated
Vaccine in CHD combined	410,112	15.69	16.26	60,981	3.00	3.10	20,300	19,684

Figure 14 Cost-effectiveness Analysis of influenza vaccination (Monte Carlo Simulation)

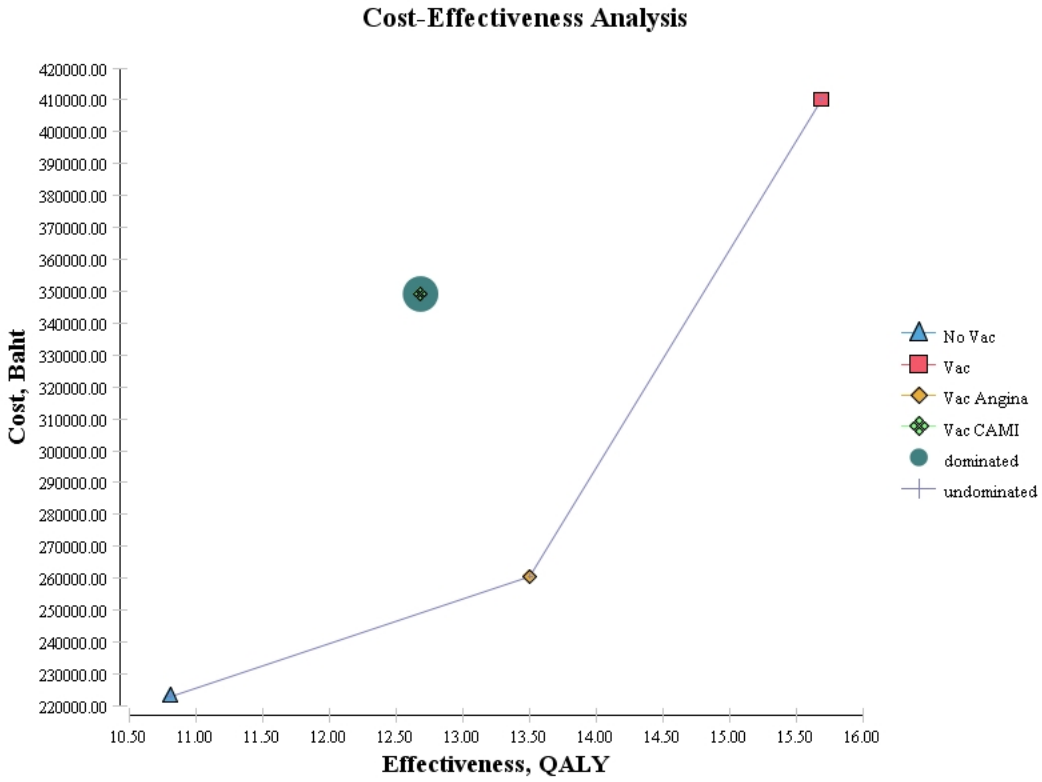


Table 14 Cost-effectiveness statistics defines 95% CI from Monte Carlo simulation compared with base case

Vaccination strategy	Total Costs (THB)		Effectiveness (QALY)	
	Base Case	95% CI	Base Case	95% CI
No Vaccination	346,437	111,010 - 357,307	18.26	5.28 - 18.20
Vaccination in Angina patients	360,786	134,448 - 407,285	19.96	7.41 - 20.06
Vaccination in patients with history of CAMI	437,901	180,215 - 497,425	19.72	6.32 -19.93
Vaccination in CHD combined group	454,664	201,067 - 630,761	21.46	8.28 - 22.21

The results representing by an incremental cost-effectiveness scatterplots (Figure 15a, b, c) demonstrating 10,000 trials from the Monte Carlo simulation. Each trial iteration compared incremental costs and effectiveness between influenza vaccination and no influenza vaccination). The results of iterations fall in each quadrant from each influenza vaccination strategy are described as follows:

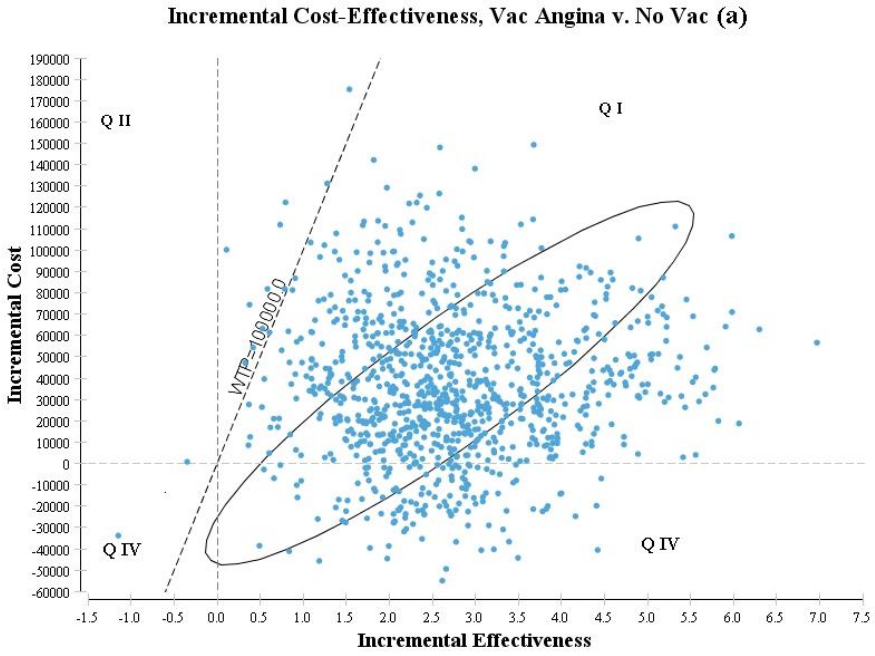
A. Influenza vaccination in Angina patients:
   a) Quadrant I contained 86.3% of the iterations, 84.9% had an ICER of less than 100,000 THB per QALY
   b) Quadrant II contained 0.19% of the iterations and all of them had an ICER of more than 100,000 THB per QALY (inferior)
   c) Quadrant III contained 0.14% of the iterations, 0.1% had an ICER of less than 100,000 THB per QALY
   d) Quadrant IV contained 13% of the iterations and all of them had an ICER of less than 100,000 THB per QALY (superior)

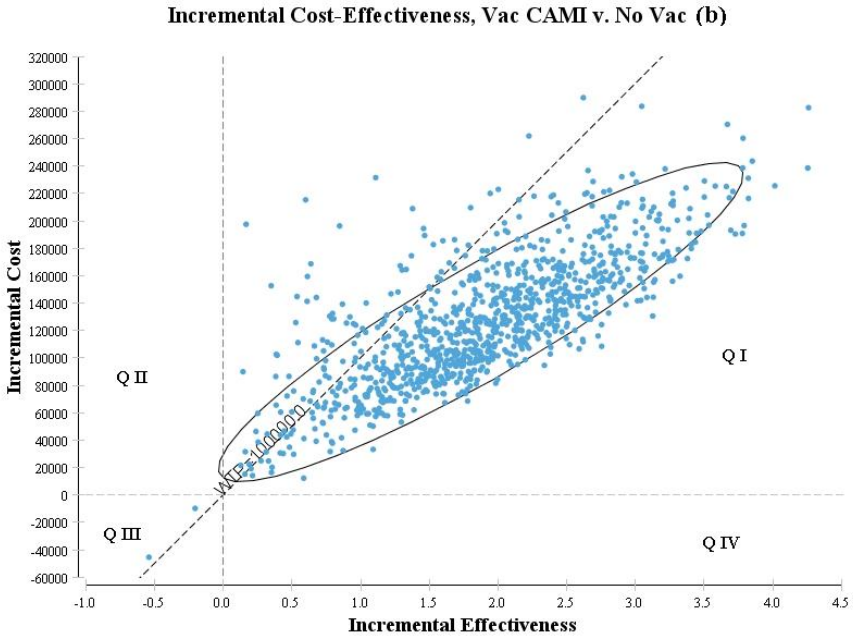
B. Influenza vaccination in CA/MI patients:
   a) Quadrant I contained 99.61% of the iterations, 89.02% had an ICER of less 100,000 THB per QALY
   b) Quadrant II contained 0.11% of the iterations, all of them had an ICER of more 100,000 THB per QALY (inferior)
   c) Quadrant III contained 0.19% of the iterations, 0.17% had an ICER of less 100,000 THB per QALY
   d) Quadrant IV contained 0.09% no iteration, all of them had an ICER of less 100,000 THB per QALY (superior)

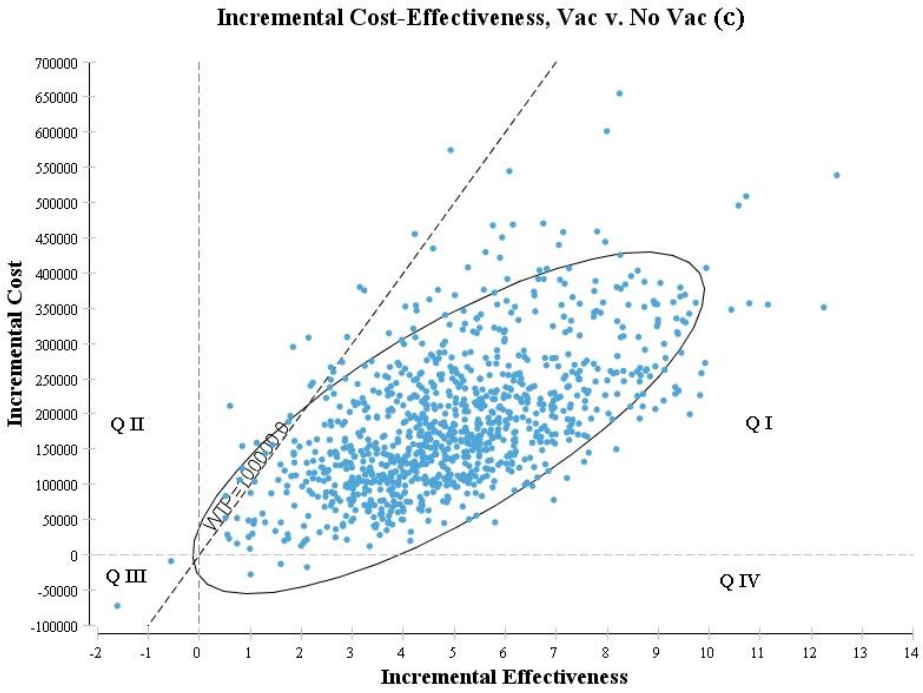
C. Influenza vaccination in CHD combined group:
   a) Quadrant I contained 99% of the iterations, 96.72% had an ICER of less 100,000 THB per QALY

b) Quadrant II contained 0.16% of the iterations, all of them had an ICER of more than 100,000 THB per QALY (inferior)
c) Quadrant III contained 0.15% of the iterations, 0.12% had an ICER of less 100,000 THB per QALY
d) Quadrant IV contained 0.6% of the iterations, all of them had an ICER of less than 100,000 THB per QALY (superior)

Figure 15 Incremental Cost-Effectiveness Scatterplots of influenza vaccination (a: in Angina patients, b: in patients with history of CA/MI, and c: in CHD combined group) vs. no influenza vaccination

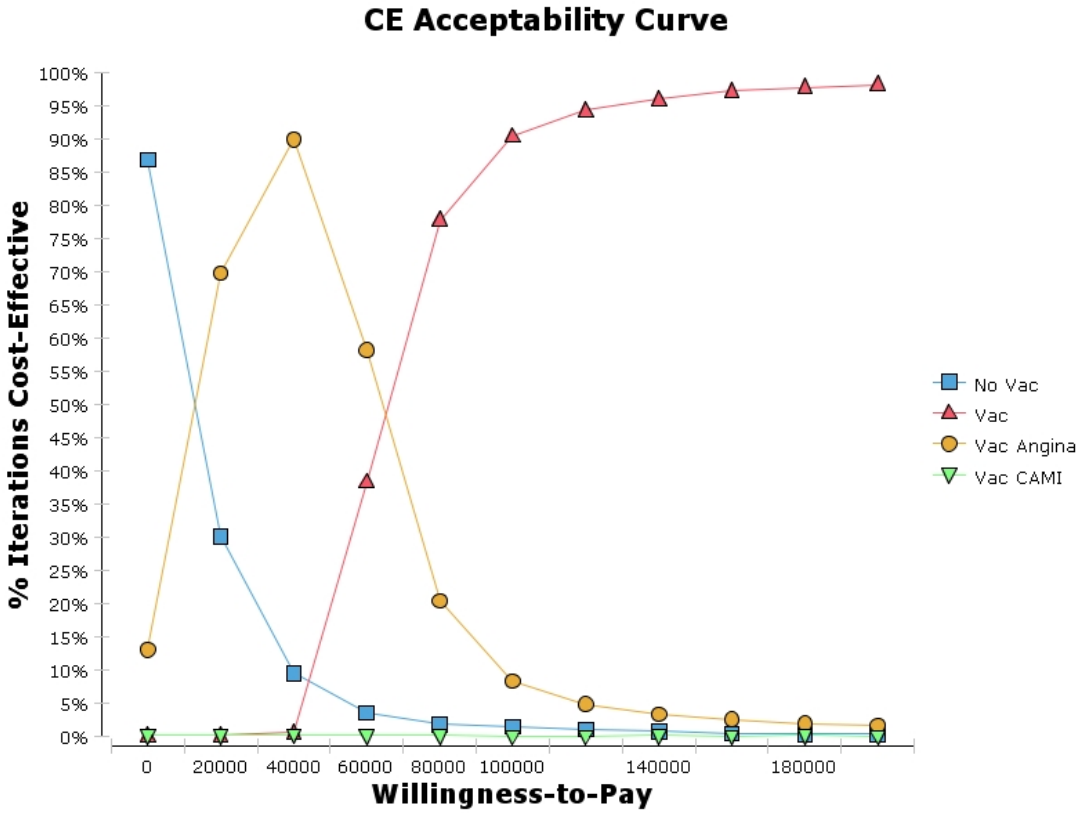






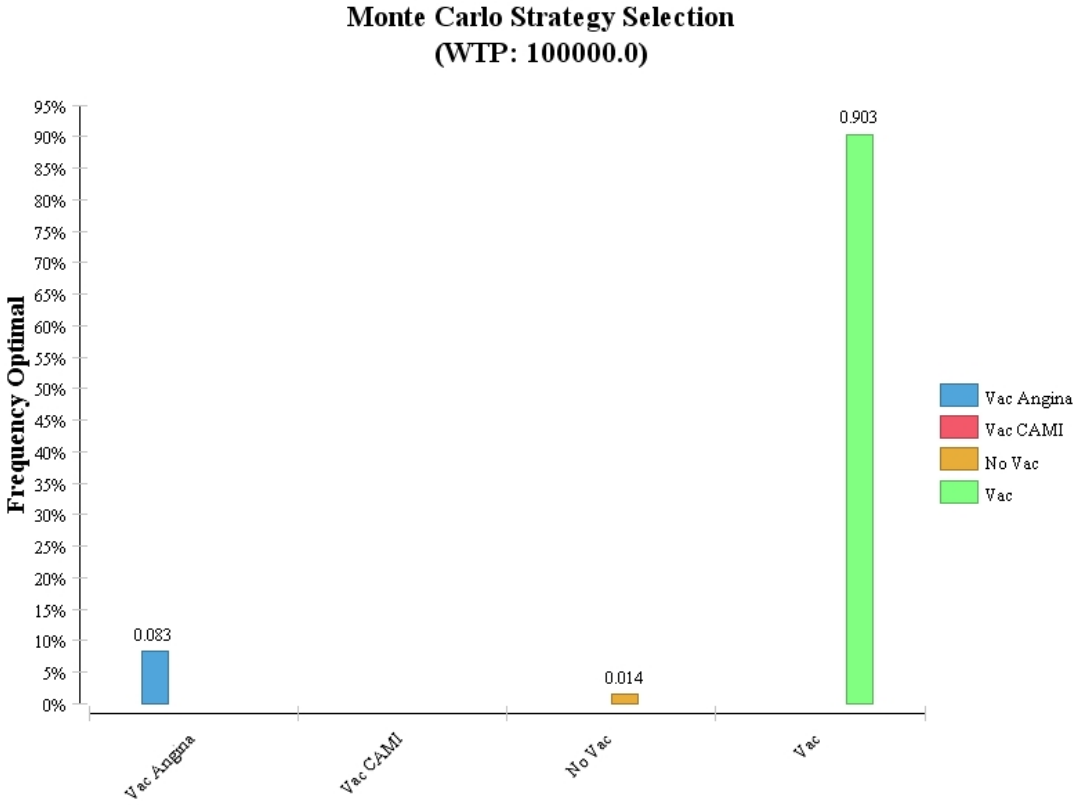
Cost-effectiveness acceptability curve was presented to shows the percentage of PSA iterations that find one or the other influenza vaccination option optimal given different willingness to pay (WTP) values. As shown in Figure 16, the cost-effectiveness acceptability curves by influenza vaccination strategy indicates that if WTP is less than 15,000 THB per QALY, the most cost effective influenza vaccinaton strategy is likely to be no vaccination. For WTP over 15,000 THB per QALY, influenza vaccination in Angina patients becomes the most cost effective and given the uncertainty present, this strategy can be 90% certain to be the most cost effective. If the WTP is more than 65,000 THB per QALY, the most cost effective influenza vaccination strategy is likely to be in CHD combined group. Given the uncertainty present, this strategy can be almost 100% certain to be the most cost effective.

Figure 16 Cost Effectiveness Acceptability Curve for lifelong influenza vaccination



If we consider willingness-to-pay threshold at 100,000 THB per QALY as used by the Thai National Formulary 2010, then the infleunza vaccination in CHD combined group would become the most cost effective demonstrating 90.3% frequency optimal as shown in figure 17.

Figure 17 Monte Carlo Strategy Selection at WTP threshold 100,000 THB per QALY



Post Hoc Analysis

The influence of age on CHD transition probabilities was observed while analyzing the study data; CHD transition probabilities were increased by age. Therefore, a Post Hoc analysis was performed to explore if age of commencing influenza vaccine would have any impact on cost-effectiveness result. Patients were stratified by their age group at 10-year range which is in accordance with the age range reported for CHD transition probabilities i.e. 35-44, 45-54, 55-64, 65-74, and 75+. Then the analyses were performed with these different age ranges. The age specific analyses showed different pattern in different vaccination strategies as follows:

1. Vaccination strategy in Angina patients : Cost-effectiveness in this influenza vaccination strategy decreased progressively by age and reached the lowest cost-effectiveness when influenza vaccine commenced at age 55. Then cost-effectiveness became gradually increased but with slower rate. As a result, the highest cost-effectiveness was found when influenza vaccine was commenced at age 35 years old.

2. Vaccination strategy in CA/MI : Cost-effectiveness in this influenza vaccination strategy gradually decreased by age and reach the lowest level when commenced influenza vaccination at age 55. Then cost-effectiveness was progressively increased with rapidly changed when commenced influenza vaccination at age 75 which led to the highest cost-effectiveness.

3. Vaccination strategy in CHD combined group : Same pattern as influenza vaccination in CA/MI patients was also demonstrated in this group.

Table 15 Comparison of Cost-Effectiveness of influenza vaccination strategies in CHD patients at different age group

Age	No Vaccine			Vaccine in Angina			Vaccine in CAMI			Vaccine in CHD combined		
	Total Cost (THB)	Total eff. (QALYs)	ICER/ QALY Gained	Total Cost (THB)	Total eff (QALYs)	ICER/ QALY Gained	Total Cost (THB)	Total eff (QALYs)	ICER/ QALY Gained	Total Cost (THB)	Total eff. (QALYs)	ICER/ QALY Gained
35-80	346,437	18.26		360,786	19.96	8,420	437,901	19.72	62,711	454,664	21.46	33,813
45-80	301,325	14.73		319,267	16.59	9,664	397,216	16.24	63,335	418,492	18.15	34,224
55-80	227,445	11.04		251,139	12.91	12,670	309,620	12.32	64,017	338,070	14.27	34,255
65-80	142,212	7.07		162,229	8.66	12,603	197,808	7.94	63,801	221,086	9.58	31,386
75-80	54,815	3.14		61,550	3.71	11,681	68,951	3.38	57,424	75,992	3.97	25,555

CHAPTER V

CONCLUSION AND RECOMMENDATIONS

This chapter provides discussion, conclusion and limitation of the study, and recommendation. There were 3 parts of discussion, first part is about the study results and their robustness as well as results interpretation. Second part is about the influencing factors to the cost-effectiveness results and the last part is about the comparison the study result with other cost-effectiveness analysis conducted previously in the similar population and standard guidelines for influenza vaccination. The limitations of the study include limitation due to nature of model based study and data unavailability. The recommendations include dissemination of study findings and future primary research.

1. Discussion

The results indicate cost effectiveness in all 3 influenza vaccination strategies as their ICERs are less than country's cost-effectiveness threshold at 100,000 THB per QALY which was accepted by the Thai National Formulary (TNF) 2010[83] and the highest cost-effectiveness is influenza vaccination in patients with less CHD severity i.e. Angina patients as it showed the lowest ICER among the 4 influenza vaccination strategies. In the vaccination to Angina patient strategy, our model designed to provide influenza vaccine only to Angina patient but vaccine would not be administered to the patient who progressed to CA/MI. This design is to evaluate an exclusive effect of influenza vaccination in the prevention of the 1st CA/MI. However, in the real life practice, influenza vaccination should be given to patient continuously for the sustainable preventive effect regardless of CA/MI progression.

The highest cost-effectiveness of influenza vaccination in Angina patients would interpret that protecting Angina patient from the first CA/MI occurrence is the most cost-effective strategy because after experiencing the first CA/MI, the probability of CA/MI recurrence is 3-time higher than the first one (refer to Table 8). However, influenza vaccination strategy in angina patients yielded QALY gained less than

influenza vaccination strategy in CHD combined group. As a result, influenza vaccination strategy in CHD combined group would be considered as optimal according to the recommendation by Gold et al.[84]

The results from probabilistic sensitivity analysis also showed the same conclusion as base case; therefore, the study results are robust.

Cost-effectiveness threshold at 100,000 THB per QALY was used to perform strategy selection using Monte Carlo simulation. The analysis revealed that influenza vaccination in CHD combined group showed frequency optimal at 90.3% which confirm influenza vaccination in CHD combined groups as the optimal strategy. Since the cost-effectiveness threshold used for this evaluation is accepted by TNF, therefore, it is assumed that policy maker in Thailand would accept the implementation of vaccination strategy in CHD combined group.

LYG results were in accordance with QALY gained and demonstrated only minor difference. As QALY composes of LY and utility (QALY = LG x Utility), the small difference beween LYG and QALY gained may imply that utility is not an influencing variable in this study. This implication is also in accordance with the result revealed by Tornado diagram.

The result from Post Hoc analysis showed vaccination in Angina as the highest cost-effective in all age range and the highest cost-effective was found when commencing vaccine at the youngest age (35 years old). In addition, influenza vaccination in CHD combined group showed that it still remains an optimal vaccination strategy in all age range. However, more cost-effectiveness was found in older age range. This may be a result from the higher benefit of influenza vaccination to reduce major adverse cardiac event including death and hospitalization for ACS to patient at older age whose CA/MI incidence is assumed to be high as studies by Phrommintikul et al.[74]

There are number of cost-effectiveness analyses conducted in other population groups but not specifically in CHD patients. Therefore, direct comparison with other

studies could not be performed. Comparing with other cost-effectiveness analyses in high risk population, our results are in accordance with these previous analyses (see Appendix B) and support the recommendation of NHSO and other international guidelines to provide influenza vaccination to high risk population. However, those cost-effectiveness analyses were conducted in developed countries where cost of living is higher than Thailand. There was only one cost-effectiveness analyses in South East Asia where mortality of adult child is high; however, study population in that analysis was with which disease symptoms were directly impacted by influenza infection[85] rather than gradually impacted like CHD.

Recently, there was one cost-effectiveness study in elderly with at least one of the seven chronic diseases listed in the NHSO plan for influenza vaccination conducted in Thailand. The study assessed influenza vaccine effectiveness in averting confirmed influenza infection. The study also aimed to determine influenza vaccine effectiveness in elderly who have acute MI as sub-group analysis in the reduction of re-infarction, re-hospitalization from coronary event(s), all heart complication, and death from coronary heart disease. However the result has not been published.[86]

There was also a controlled trial of serologic and clinical efficacy of influenza vaccine in post-MI and in those with stable angina pectoris which are comparable to the states in our model i.e. patients with history of CA/MI and Angina patients, respectively. The study has been completed but the result is still pending.[87] If data can be obtained in the future, model re-evaluation can be performed with these more specific data.

2. Conclusion

The results of this study clearly showed cost-effectiveness in all influenza vaccination compared to no influenza vaccination as its incremental cost-effectiveness ratios of all influenza vaccination strategies (range from 8,418 – 62,710 THB per QALY gained) were lower than cost-effectiveness threshold at 100,000 THB per QALY which is accepted by the Thai National Formulary 2010. Comparing within

influenza vaccination groups, the highest cost effectiveness was found in influenza vaccination in Angina patients.

The mathematical modeling evaluation from this study demonstrated influenza vaccination in Angina patients as the highest cost-effectiveness strategy. However, considering country cost-effectiveness threshold that is accept by TNF (100,000 THB per QALY), it shows influenza vaccination in CHD combined patients as an optimal influenza vaccination strategy. Patients' age in which influenza vaccination is commenced gave the highest influence to the study results comparing to other input variables; however, the cost-effectiveness results by age ranges still confirmed vaccination in Angina patients as the highest cost-effective and vaccination in CHD combined group as the optimal strategy across all age ranges.

3. Limitation of the Study

Like any model-based evaluation, our study synthesized data from multiple sources with assumption when data were incomplete or unavailable. The study has several limitations as follow:

3.1 CHD is a chronic disease so we developed a lifetime model to assess the lifetime costs and effectiveness of influenza vaccine strategies but influenza vaccination is a yearly intervention and effectiveness/efficacy of vaccination is generally only for one year hence lack of long-term use data. As a result this analysis may lack of many long-term data related to influenza vaccine efficacy/effectiveness.

3.2. A fixed-value parameter to estimate vaccine efficacy was applied even though the vaccine efficacy would vary from year-to-year, depending on circulating influenza strains match.

3.3. There is no influenza vaccine effectiveness in Thai CHD and the model acquired data from foreign patients. This would limit the generalizability to apply study result in Thai patients. However, we used data from systemic review (Cochrane) to enhance the credibility and generalizability of the data.

3.4 Our model divided CHD patient into 2 groups; mild severity (Angina patient) and more severe (CA/MI) but the available risk ratio/relative risk achieved by influenza vaccination used for the adjustment of CHD transition probability is only for overall CHD patients. As vaccine effect to CHD patients at different disease severity is expected, then using one data for both different severity group may prone to bias.

3.5 Costs related to CHD were obtained from single source which is a tertiary care hospital that might not be well represented the general cost in Thailand. As a result, generalizability of study results to the whole is limited. However, result from one-way sensitivity analysis demonstrated that total CHD costs contributed less than 0.1% of the overall influences incurred by all input variables.

3.6 This study hypothesized influenza infection as an accelerating factor to CHD transition but relative risk of ILI which is a surrogate of influenza infection was input into the model. However ILI is generally used for effectiveness study so the effect on using ILI data would be acceptable. Moreover, relative risk of ILI was used to estimate cost incurred by influenza infection which unit cost was only a small portion of the total cost in the model. Therefore the impact of the ILI used would be minimal.

3.7 This is lifetime modeling; therefore, it was assumed that vaccine would be administered or not administered annually lifelong without cross-over between vaccination strategies. This might not be always true in the real practice that patients may skip vaccination in some year or patients may cross-over vaccination strategies due to various reasons including the pandemic occurrence, if occur. This complex scenario with high uncertainty would limit adaptation of one single model that would be appropriate to all situations. This would be an area for future study focusing on dynamic and uncertainty model.

3.8 The non-vaccination group may be indirectly protected from influenza infection due to the effect of herd immunity as shown in the studies by Pieda et al.[88] and Grijalva et al.[89] Therefore influenza protection achieved by influenza

vaccination may be higher than the actual vaccine effectiveness. However the influence of influenza incidence to the overall costs in this model is low and therefore could be omitted.

4. Recommendations

Finding from our study recommends influenza vaccination in CHD combined groups as optimal strategy; this is in accordance with the current practice worldwide and in Thailand. Influenza vaccine underutilization has been reported recently,[9] it would be recommended to disseminate result of our study to healthcare providers so that they are fully aware of influenza vaccine cost-effectiveness benefit and then would recommend influenza vaccination to their CHD patients.

Though the result of influenza vaccine benefit to CHD patients are clearly demonstrated from economic modeling, primary clinical data in the Thai population is required in order to provide a solid recommendation at the national policy level. In particular, to implement influenza vaccination strategy to all CHD patients would require about 172,160 vaccine doses [90,91] which cost about 77.6 million THB. As such, primary economic research is recommended to support decisions at the policy level.

Mass implementation of influenza vaccine strategy at national level would reduce vaccination cost significantly due to bulk purchasing. As a result, influenza vaccine implementation would cost less than the current estimation which bases vaccine cost at market price. Therefore, cost-effectiveness should also be recalculated with the bulk purchase of vaccine at lower price.

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APPENDIX A

Extracting study results and converting to the desired format

1. Standard Error (SE)
   a. From Standard deviation (SD)

      SD = SE x $\sqrt{N}$

   b. From 95 % confidence interval

      SE = (upper limit – lower limit) / 3.92

2. SE of Risk Ratio (Relative Risk, Odds Ratio, Hazard Ratio)
   a. From confidence interval

   lower limit = ln (lower confidence limit given for RR)

   upper limit = ln (upper confidence limit given for RR)

3. Standard deviation (SD)
   a. From 95 % confidence interval

      SD = $\sqrt{N}$ x (upper limit – lower limit) / 3.92

   b. From interquartile range

   SD = interquartile range /1.35

4. Relative risk (RR) from events in clinical study
   a. RR = (a/(a+b))/(c/(c+d))
5. SE of Relative Risk from events in clinical study
   a. SE (ln RR) = $\sqrt{\frac{1}{a} - \frac{1}{(a+b)} + \frac{1}{c} - \frac{1}{(c+d)}}$
6. Costs
   a. Estimation of SD from mean

      SD = 0.125 x mean[i]

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APPENDIX B

Summary of Cost Utility Evaluation

Ref	Stanciole 2012
Population	COPD & Asthma
Main outcome measures	Cost/DALY avert
Design/Methods	Economic model -lifetime
Setting	Sub-Saharan Africa (AfrE) and SE Asia (SearD)
Data sources	1. Disease rates and profiles : WHO Global Burden of disease study 2. Estimated intervention effects and resource needs : clinical trials, observational studies, treatment guidelines 3. Unit costs : WHO price database
Strategies	1. Low dose inhaled corticosteroids (ICS) for mild persistent asthma 2. Flu vaccination for COPD 3. Low dose ICS plus long acting β agonists (LABA) for moderate persistent asthma
Conclusion	1. For mild persistent Asthma : the most cost effective intervention is low-dose ICS 2. COPD : Sear-D - the most cost effective intervention is influenza vaccination in 3. For moderate persistent asthma : the most cost effective intervention is ICS plus LABA in Afr-E
Perspective	Governmental & Health care payer
Sensitivity	1. DSA : one-way 2. PSA : CE plane

APPENDIX B

Ref	Fisman 2011	Myers 2011
Population	General population	Pregnancy (timing of vaccination)
Main outcome measures	ICER/QALY gained	Health and economic outcomes during the 12-Mo
Design/Methods	Economic model - 10 years Used TreeAge	Economic model -Markov - weekly cycle - 12 months
Setting	Canada	US
Data sources	Published literature	1. No. & gestational age distribution for pregnant women and infant : National Center of Health Statistics 2. Published literature
Strategies	1. Unadjuvanted TIV (cur practice) 2. MF59-adjuvanted influenza vaccination in adults $\geq$ 65 years 3. Adjuvanted influenza vaccination in both old adults and child < 6 years	1. Influenza vaccine 2. No influenza vaccine
Conclusion	Replacement of traditional TIV with MF59-adjuvanted vaccine would confer substantial benefits to vaccinated and unvaccinated individuals and be economically attractive relative to other widely-used preventive intervention	Influenza vaccination provided the greatest benefit (to both mother and infant) if vaccinated early of influenza season.
Perspective	Health care payer	Societal
Sensitivity	DSA : one-way	DSA : uni- and multivariate

APPENDIX B

Ref	Lee 2011	Prosser 2011
Population	Adult hemodialysis patient	Healthy children Aged 6 months to 4 Years
Main outcome measures	ICER/QALY gained	1. ICER/QALY gained 2. Vaccine cost 3. Clinical flu-related events averted/1000 vaccine children 4. dollars/ flu related event avoided 5. Dollars/ hospitalized or death avoided/ averted
Design/Methods	Economic model - 1 year Used TreeAge	Economic model & long-term effects of influenza & vaccines
Setting	US	Primary care in US
Data sources	Published literature	Published literature and supplemented by expert opinion when data were limited
Strategies	1. Adjuvanted flu vaccine at different cost and efficacy 2. Nonadjuvanted influenza vaccination	1. No influenza vaccination; 2. IIV 3. LAIV.
Conclusion	Adjuvanted influenza vaccination with adjuvanted cost $\leq$2 $ could be a cost-effective strategy in a standard flu season depending on the potency of adjuvanted vaccine	LAIV had comparable cost-effectiveness compared with IIV for children < 5 years
Perspective	Societal	Societal
Sensitivity	1. DSA : Tornado 2. PSA : CEAC	1. DSA - one-way 2. PSA

APPENDIX B

Ref	Lin 2009	Brydak 2012
Population	Adult cancer	adults aged ≥65 years
Main outcome measures	ICER/influenza case prevented and LYG	1. Total program cost 2. Cases averted 3. ICER/QALY
Design/Methods	Economic model	Economic model - 1 year
Setting	Taiwan National Cancer Registry in 2002	Poland
Data sources	1. Published and unpublished sources 2. No. of cancer patients : Taiwan National Cancer Registry	1. Published literature 2. Central Statistic Office of Poland and validated by Polish expert opinion
Strategies	1. Influenza vaccine 2. No influenza vaccine	1. Influenza vaccine 2. No influenza vaccine
Conclusion	Influenza immunization for cancer patients is cost-saving and cost-effective from a healthcare and societal perspective in Taiwan. Therefore annual influenza vaccinations for this patient group is highly recommended	Implementing a vaccination program would be a very cost-effective strategy.
type of source of data	secondary data (including Taiwanese database)	secondary data (including Polish database)
Perspective	healthcare system and society	National Health Insurance
Sensitivity	DSA : one-way - Tornado diagram	1. DSA - Tornado diagram 2. PSA - CE plane, CE acceptability curve

APPENDIX B

Ref	Nosyk 2011	Lee 2012
Population	HIV	Pediatric (2-18 years)
Main outcome measures	ICER and EVPI	Cost & effectiveness
Design/Methods	RCT, multi-centered - Markov cohort model - monthly cycle - one-year vaccinating and lifetime costs and health-related QoL	Economic model - Multi year
Setting	12 Canadian HIV trials Network sites	No information
Data sources	1. Transition probability bet. states, mortality (influenza): systematic review 2. Utility & Cost of ILI : collected prospectively among patients enrolled into this study; utility declined due to ILI was from literature	
Strategies	A) 2 standard doses over 28 days B) 2 double doses over 28 days C) a single standard dose D) Standard dose vaccination (control)	1. Universal flu vaccine lifetime 2. Standard annual influenza vaccine
Conclusion	Study results do not support a policy to implement increased antigen dose/ booster dosing strategies with seasonal, inactivated trivalent, non-adjuvanted intramuscular vaccine for individuals with HIV in Canada.	Universal influenza vaccine would cost effective in certain conditions (vaccine cost, effectiveness, protective duration)
Perspective	Societal	No information
Sensitivity	1. DSA : one-way 2. PSA: CEAC	

APPENDIX B

Ref	Hibbert 2007	Avritscher 2007
Population	Adult aged 50-64	Young children
Main outcome measures	Health outcome and costs	1. Cost saved/case averted 2. QALY gained/100,000 vaccinated children
Design/Methods	Economic model - 1 year	Economic model
Setting	Australia	Day-care centre in US
Data sources	1. ILI : Health database 2. Hospitalization and mortality : published literature 3. Vaccine eff : Cochrane review 4. Utility : Australian study 5. Cost : Australian Refined Diagnosis Related Group	1. Published literature 2. Costs of vaccination : CDC vaccine price list, admin cost from published literature 3. QALY : published literature
Strategies	1. Universal Flu vaccine (50+- yrs) 2. Standard annual Flu vaccine $\underline{\geq}$ 65 yrs	1. Influenza vaccination 2. No vaccination
Conclusion	From all the perspectives: a new Flu vaccination policy was more costly & more effective	Immunization with LAIV-T was cost saving from a societal perspective in both seasons
Perspective	Healthcare payer & societal	Societal
Sensitivity	1. DSA : tornado and graph show relationship of vaccine cost and ICER 2. PSA : CEAC	DSA : one-way

APPENDIX B

Ref	Avritscher 2007
Population	Working-age cancer patients
Main outcome measures	ICER/QALY gained
Design/Methods	Economic model
Setting	US
Data sources	1. Published sources, supplemented with data collected from the authors' own institutional accounting system. 2. Sero-conversion in adult cancer patients after immunization : meta-analysis of 6 published studies
Strategies	1. Influenza vaccination 2. No vaccination
Conclusion	All working-age cancer patients who are within 5 years of cancer diagnosis and have a life expectancy of at least 3 months should be vaccinated against influenza
Perspective	Societal
Sensitivity	DSA : one-way & two-ways

APPENDIX B

Ref	Marchetti 2007
Population	Children 6 to 60 months
Main outcome measures	ICER/QALY gained
Design/Methods	Economic model -Markov model - 5 influenza seasons
Setting	Italy - Cohort of 3 million children and their households
Data sources	1. ILI and ILI-related events : national passive surveillance network, INFLUNET 2. Attack rates : average of values available for the last two influenza seasons 3. AOM, Hospitalization rates, Vaccine effectiveness: published literature 4. ILI-related fatality rate in children: assumed = 0 5. Rate of ILI in households : assumed 6. Health care costs : assumed 7. Utility : Australian Bureau
Strategies	1. Immunization of children at "high risk" (Current practice) 2. Vaccination of 6–60 mos. 3. Vaccination of 6–24 mos.
Conclusion	Universal vaccination of 6–60-month-old children with a virosomal adjuvanted influenza vaccine is cost saving for the society and is highly cost-effective for health care system. National and regional policies should strongly consider the adoption of such immunization programs.
Perspective	Italian society health care
Sensitivity	1) DSA : one-way 2) PSA

APPENDIX B

Ref	UCHIYAMA 2006	Roberts 2006
Population	Elderly (influenza & pneumococcal)	Pregnant women
Main outcome measures	ICER/LYG	1. Cost saved 2. Quality adjusted hours (QAH)
Design/Methods	Economic model - 1 year	Economic model - 1 year -
Setting	Japan	US
Data sources	1. Published literature 2. Public organizations,	Costs associated with influenza virus infection and its complications : 2002 Healthcare Cost and Utilization Project
Strategies	1. No influenza vaccination 2. Influenza vaccine only 3. Influenza + pneumococcal vaccine	1. Vaccination all pregnant women with inactivated trivalent influenza vaccine (ITV) for 1 influenza season 2. Provision of supportive care only
Conclusion	Combined vaccinations would be more cost-effective than the vaccination for influenza only.	Universal vaccination with ITV is cost-saving relative to providing supportive care alone in the pregnant population.
Perspective	Societal	Societal
Sensitivity	PSA	DSA : Tornado , one-way, bivariate

APPENDIX B

Ref	Allsup 2004	Wood 2000
Population	Healthy ages 65 -74	Healthy working-age adults
Main outcome measures	ICER/QALY gained	Cost benefit
Design/Methods	Primary research (RCT)	Literature review
Setting	Primary care in UK	6 published PE
Data sources	Primary data	1. 3 prospective studies 2. 1 retrospective study 3. 2 model based simulations
Strategies	1. 23-valent-pneumococcal polysaccharide vaccine & influenza vaccine 2. 23-valent-pneumococcal polysaccharide vaccine	1. Influenza vaccination 2. No influenza vaccination
Conclusion	Influenza vaccination in this population would not be cost effective (study was under powered due to study was premature termination and influenza activity during the study period was not high)	Influenza vac in the healthy, working adult would be a cost-effective but decision makers have not yet extended existing recommendations due to disparity among economic studies in their methods
Perspective	NHS	Employer & Societal
Sensitivity	DSA	NA

APPENDIX B

Ref	Lee 2010	Postma 2005
Population	children (administration timing)	Healthy working adults
Main outcome measures	Costs and QALY	Cost averted
Design/Methods	Economic model - Monte Carlo	Economic model
Setting	US	Netherlands
Data sources	1. vaccine cost, OTC medication : average wholesale price 2. Hospitalization for flu : National Inpatient Survey of the Healthcare Cost and Utilization Project 3. Influenza & vaccine efficacy, OPD cost: Cochrane review 4. Utility : Triangular distribution	Published literature, databases and expert opinions
Strategies	1. Influenza vaccination (monthly timing) 2. No influenza vaccination	1. Influenza vaccination 2. No influenza vac/no treatment 3. No influenza vaccination &tx
Conclusion	Policymakers could invest up to $6 million to $9 million a year to get children vaccinated in Sep or Oct without expending any net costs.	Consistent picture of net cost savings for prevention through vaccination and Oseltamivir treatment
Perspective	Societal & Third-party payers	societal
Sensitivity	1) DSA 2) PSA	PSA : EC plane

APPENDIX B

Ref	Allsup 2003	Zubareva 1976
Population	Aged 65-74 (no high risk factor)	[Epidemiological and economic evaluation of the effectiveness of immunization with live influenza vaccine during the influenza epidemic of 1971-1973 in the city of Frunze] - data is not available
Main outcome measures	1) GP attendance with ILI or pneumonia 2) Respiratory symp, hosp/death 3) self-reported ILI 4) QoL 5) Adverse reaction	
Design/Methods	Primary research (RCT)	
Setting	Primary care in UK	
Data sources	Primary data (RCT)	
Strategies	1) Influenza vaccination 2) No influenza vaccination	
Conclusion	No difference between groups for the primary outcome measure due to underpowered. Vaccination had no significant effect on any of the QoL measures used, although vaccinated individuals were less likely to self-report ILI.	
Perspective	Societal	
Sensitivity	DSA	

APPENDIX B

Ref	Sande 2010	Postma 1999
Population	Entire population	Elderly aged > 65 and chronically ill elderly
Main outcome measures	ICER/QALY gained	ICER/LYG
Design/Methods	Cost evaluation in companion with ecological study	Economic model
Setting	Ontario/Canada	The Netherlands
Data sources	1. Prior epidemiological study that compared outcomes in Ontario before and after universal immunization 2. Ontario health administrative data	1. Published literature 2. Dutch Central Bureau of Statistics 3. Cost : Dutch guiders, registration of hospitalization
Strategies	1. UIIP 2. TIIP	Influenza vaccination
Conclusion	Universal immunization against seasonal influenza was estimated to be an economically attractive intervention.	Influenza vaccination has a cost-effectiveness ratio that is better than or comparable to that of other implemented Dutch programs in the prevention of infectious diseases.
Perspective	Health care payer	Health care
Sensitivity	1. DSA - one-way - Tornado 2. PSA - Incremental cost acceptability curve	DSA

APPENDIX B

Ref	Lannazzo 2011	Tuccillo 2003
Population	Elderly	Health personnel
Main outcome measures	Cost	1. ILI case 2. Sickness absence 3. Cost
Design/Methods	Economic model	data not available
Setting	Italy	Italy
Data sources	1. Health economics and demographic data : specific Italian sources 2. Vaccine effectiveness data : published literature 3. Direct med costs : cur Italian prices & tariffs	data is not available
Strategies	1. Standard vaccination 2. MF59 adjuvanted vaccine 3. No vaccination	
Conclusion	The MF59 adjuvanted vaccine resulted more effective and cost saving comparing with the std. vaccination and with no vaccination. The std. vaccine, even though a light cost increase, still proved to be effective compared to the null option (initial vaccination program cost nearly offset by healthcare resources savings (during the season)	
Perspective	data is not available	
Sensitivity		

APPENDIX B

Ref	Weaver 2001	Prosser 2006
Population	Aged > 65 years (combined outreach for Pneumococcal and influenza vaccine)	Children stratified into 10 sub-groups by age and risk
Main outcome measures	ICER/QALY gained	ICER/QALY gained
Design/Methods	Primary research (RCT) , - TreeAge	Economic model - 1 year -
Setting	Primary care in US	US
Data sources	1. Primary data 2. Effectiveness of vaccine and cost of treatment : published estimation	1. Published literature and were supplemented by expert opinion where data were limited or unavailable 2. Health care costs : Health insurance database
Strategies	1. Influenza vaccine 2. Pneumococcal vaccine 3. Combined outreach	1. No vaccination 2. IIV 3. LAIV
Conclusion	The community-based outreach initiative to promote the pneumococcal and influenza vaccines was reasonably cost-effective.	Risk status was more important than age and vaccination was less cost-effective as the child's age increased. Vaccination of all children is less cost-effective than of all children ages 6–23 months & all children at high risk.
Perspective	Societal	Societal
Sensitivity	DSA : one-way	1. DSA - Tornado 2. PSA - CEAC

APPENDIX B

Ref	Nichol 2001	Clements 2011
Population	Working adults (18-64 years)	General specified by age group
Main outcome measures	Net costs or saving	ICER/QALY gained
Design/Methods	Economic model	Economic modeling (age specified)
Setting	US	US
Data sources	Published literature	1. Published literature 2. CDC vaccine price list 3. Physician fee and coding guideline 4. Red book
Strategies	1. No vaccination 2. IIV	1. UMV 2. TVP
Conclusion	Influenza vaccination of healthy working adults on average is cost saving. These findings support a strategy of routine, annual vaccination for this group, especially when vaccination occurs in efficient and low-costs sites	UMV against seasonal influenza is cost saving in the United States under reasonable assumptions for coverage, cost, and efficacy
Perspective	Societal	Societal
Sensitivity	DSA : Tornado diagram	1) DSA 2) PSA

APPENDIX B

Ref	Prosser 2011	Hoek 2011
Population	all age (H1N1)	All age (H1N1)
Main outcome measures	ICER/QALY gained	QALY
Design/Methods	Economic model - 1 year &longer-term costs and consequences of long-term squeal deaths	Prospective population based study
Setting	US	UK
Data sources	1. Emerging primary data on pH1N1 infections in the US 2. Published and unpublished data and supplemented by expert opinion	Primary data but result compared with seasonal influenza form a systematic literature review
Strategies	1. No vaccination 2. IIV	NA
Conclusion	Vaccination (pH1N1) in children and working-age adults is cost-effective compared to other preventive health interventions (wide range scenarios). This was consistent with target recommendations. Delays in vaccine availability had a substantial impact on the cost-effectiveness of vaccination.	QALY loss was minor for individual patients; the estimated total burden of influenza over the pandemic was substantial when compared to other infectious diseases.
Perspective	Societal	NA
Sensitivity	DSA	NA

APPENDIX B

Ref	Jit 2011	Smith 2010
Population	Pregnant women	50 yrs
Main outcome measures	ICER/QALY gained	Cost/QALY
Design/Methods	Economic model -TreeAge	Economic model - Markov model-10 years
Setting	UK	US
Data sources	1. Published literature 2. Hospital Episode Statistic 3. Laboratory reports 4. Data on file & RCGP 5. Gen. Practice Research DB	1. Published literature 2. Estimation
Strategies	1. No vaccination 2. Influenza vaccine, timing	1. No vaccination 2. PPV only 3. Influenza vaccine 4. Dual vaccines 5. CDC recommended*
Conclusion	Vaccinating pregnant women against seasonal influenza may be cost-effective, with ICER ~£23,000, assuming protection for a single season and some benefit to infants.	Dual vaccination of all 50-year-olds economically reasonable. Shorter duration models may not fully account for PPV effectiveness
Perspective	1. Health service 2. 3rd payer	Societal
Sensitivity	1) DSA - univariate, tornado 2) PSA - EC acceptability curve	1) DSA – one and multi 2) PSA - CEAC

APPENDIX B

Ref	Khazeni 2009	Luce 2008
Population	Residents of a U.S. metropolitan	Aged 24-59 months
Main outcome measures	Infections and deaths averted, costs, QALYs, ICER	Cost
Design/Methods	Economic model - Markov model	Economic model
Setting	US	US
Data sources	Literature and expert opinion	1. Patient level data : clinical trial 2. Cost data : published literature
Strategies	1. Stockpiled strategy 2. Expanded prophylaxis strategy), 3. Expanded vaccination strategy	1. LAIV 2. TIV
Conclusion	Expanded adjuvanted vaccination is an effective and cost-effective mitigation strategy for an influenza A (H5N1) pandemic. Expanded antiviral prophylaxis can help delay the pandemic while additional strategies are implemented.	Due to its increased relative vaccine efficacy over TIV, LAIV reduced the burden of influenza and lowered both direct health care and societal costs among children 24–59 months of age.
Perspective	Societal	Societal
Sensitivity	NA	1) DSA - one-way 2) PSA - CE plane

APPENDIX B

Ref	Aballea 2007 - Spain	Aballéa 2007 - International
Population	Aged 50-64	Age 50-64
Main outcome measures	ICER/QALY gained	1. Cost and clinical outcome 2. ICER/QALY gained
Design/Methods	Economic model	Economic model
Setting	Spain	International
Data sources	Published literature and validated through expert opinion	Published literature
Strategies	1. Influenza vaccination to 50 - 64 years (proposed policy) 2. Influenza vaccination to ≥ 65 year (current policy)	1. Vaccine in high risk (current policy) 2. Vaccine in age 50 -64 (proposed policy)
Conclusion	From societal perspective, the corresponding results were € 4149/ QALY and € 2706 per LYG. Extending routine influenza vaccination to people over 50 years of age is likely to be cost-effective.	Extending routine influenza vaccination to people more than 50 years of age is likely to be cost-effective in all four countries studied.
Perspective	1. Third payer 2. Societal	1. Third payer 2. Societal
Sensitivity	1. DSA - Tornado 2. PSA -CE acceptability curve	1. DSA - Tornado 2. PSA - CE acceptability curve

APPENDIX B

Ref	Maciosek 2006	Turner 2006
Population	Ag 50-64 and 65 and older	aged 50-64
Main outcome measures	1. Effectiveness and Cost effectiveness 2. Burden of disease and cost	1. Cost 2. QALY 3. Reductions in influenza cases
Design/Methods	systematic of secondary data	Economic model - decision tree
Setting	US	UK
Data sources	Published literature	1. Published literature 2. Cost of vaccination : Prescription Pricing Authority and vaccination cost, British National Formulary
Strategies	Vaccine and no vaccine	1. No vaccination 2. Influenza vaccination
Conclusion	1. Influenza vaccination is a high-impact, cost-effective service for persons aged $\geq$ 65 2. Vaccinations are also cost effective for persons aged 50 to 64.	Extension of the current immunization policy has the potential to generate a significant health benefit at a comparatively low cost.
Perspective	Societal	1. NHS 2. Societal
Sensitivity	DSA : uni and multivariate	1. DSA - One-way 2. PSA - CE acceptability curve

Abbreviations:

AfrE : Countries in sub-Saharan Africa with very high adult and high child mortality

SearD : Countries in South East Asia with high adult and high child mortality

IIV : Inactivated influenza vaccine

LAIV : Live, attenuated influenza vaccine

CEAC : Cost-effectiveness acceptability curve

UIIP : Universal Influenza Immunization Program

TIIP : Targeted influenza immunization program

UMV : Universal mass vaccination

TVP : Targeted vaccine program

PPV : Pneumococcal polysaccharide vaccine

RCGP : Royal College of General Practitioners

Stockpiled strategy : Vaccination and antiviral therapy in quantities similar to those currently available in the U.S. stockpile

CDC recommended strategy : Influenza vaccination for all, PPV when comorbid conditions are present

LYG : Life Year Gained

APPENDIX C

ดัชนีราคาผู้บริโภค

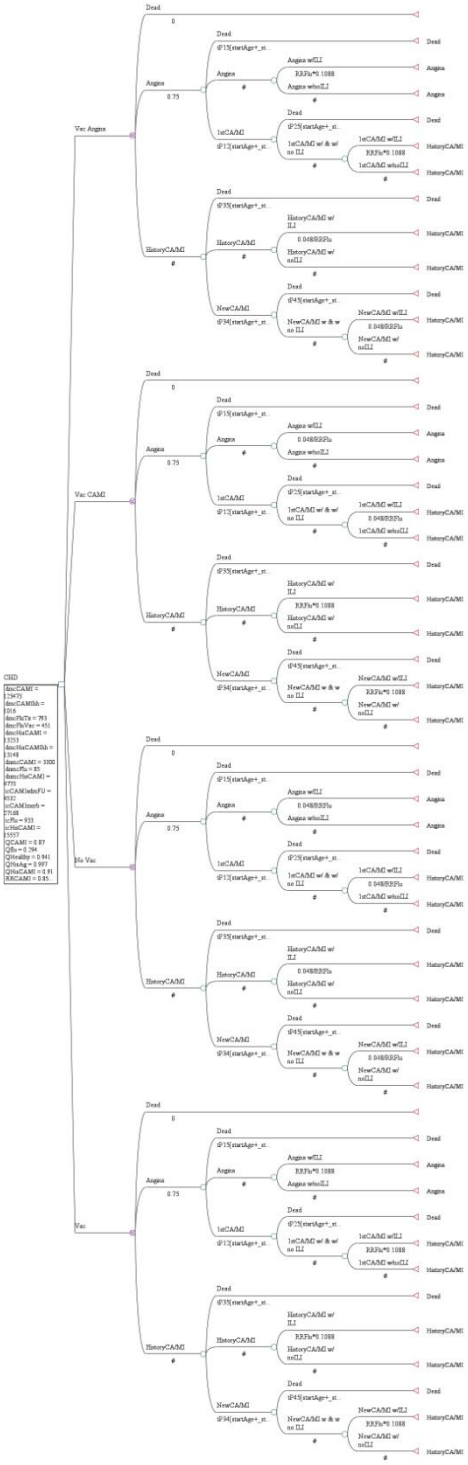
ปี	CPI (all commodities)	CPI (Medicare)
2520	24.6	25.3
2521	26.6	27.4
2522	29.2	29.1
2523	35	36.9
2524	39.4	40
2525	41.4	42.5
2526	43	44.1
2527	43.4	45.2
2528	44.4	46.6
2529	45.2	47.1
2530	46.3	48.3
2531	48.1	49.2
2532	50.7	52
2533	53.7	56.3
2534	58.8	59.9
2535	59.1	64.4
2536	61.1	70.2
2537	64.2	75.4
2538	67.9	78.1
2539	71.8	79.2
2540	75.9	81.8
2541	82	86.4
2542	82.2	88.6
2543	83.5	90.2
2544	84.9	92.3
2545	85.4	93.4
2546	87	94.6
2547	89.4	96.8
2548	93.4	98.5
2549	97.8	99.5
2550	100	100
2551	105.4	100.5
2552	104.5	100.9
2553	108.0	101.1

ที่มา สำนักดัชนีเศรษฐกิจารค้า กระทรวงพาณิชย์

APPENDIX D

Screenshots

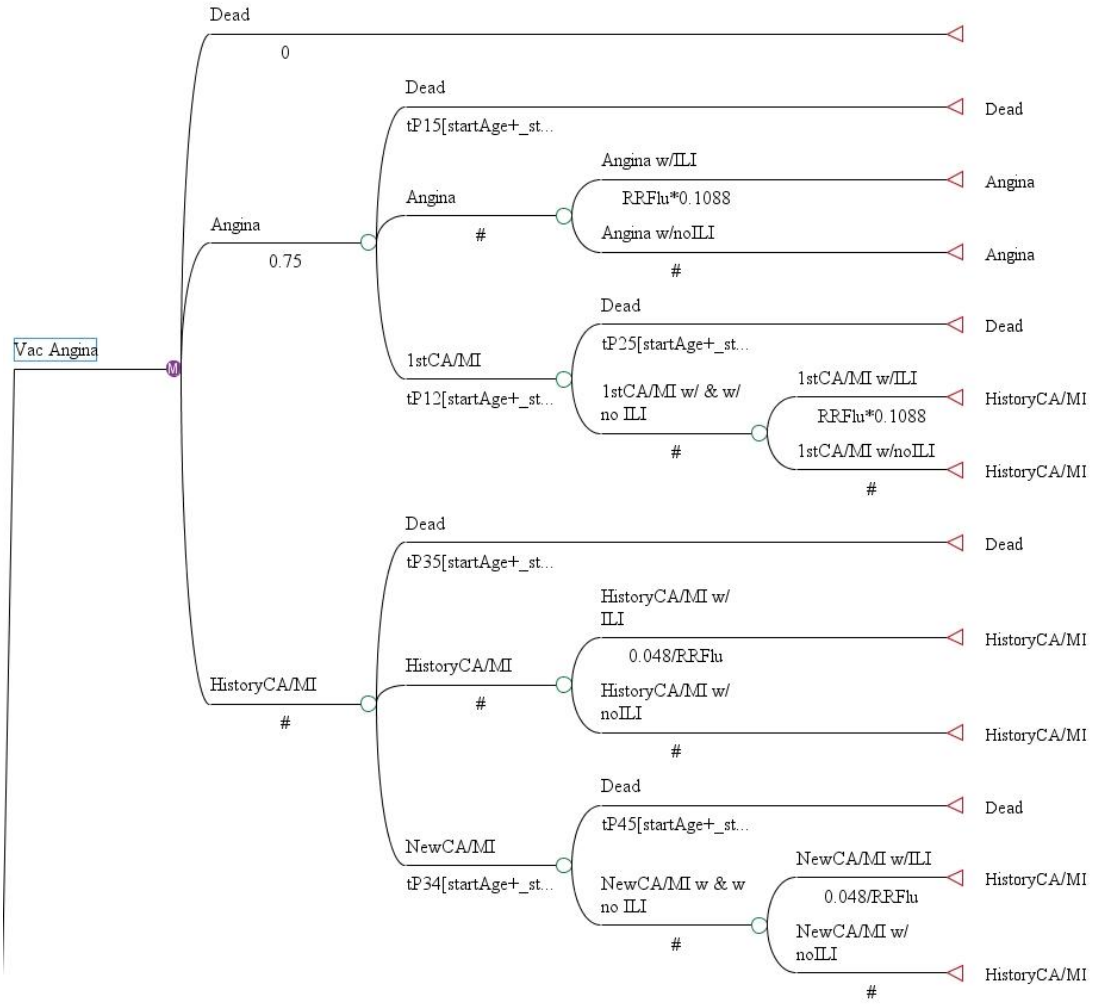
Decision tree model



APPENDIX D

Screenshots (Continue)

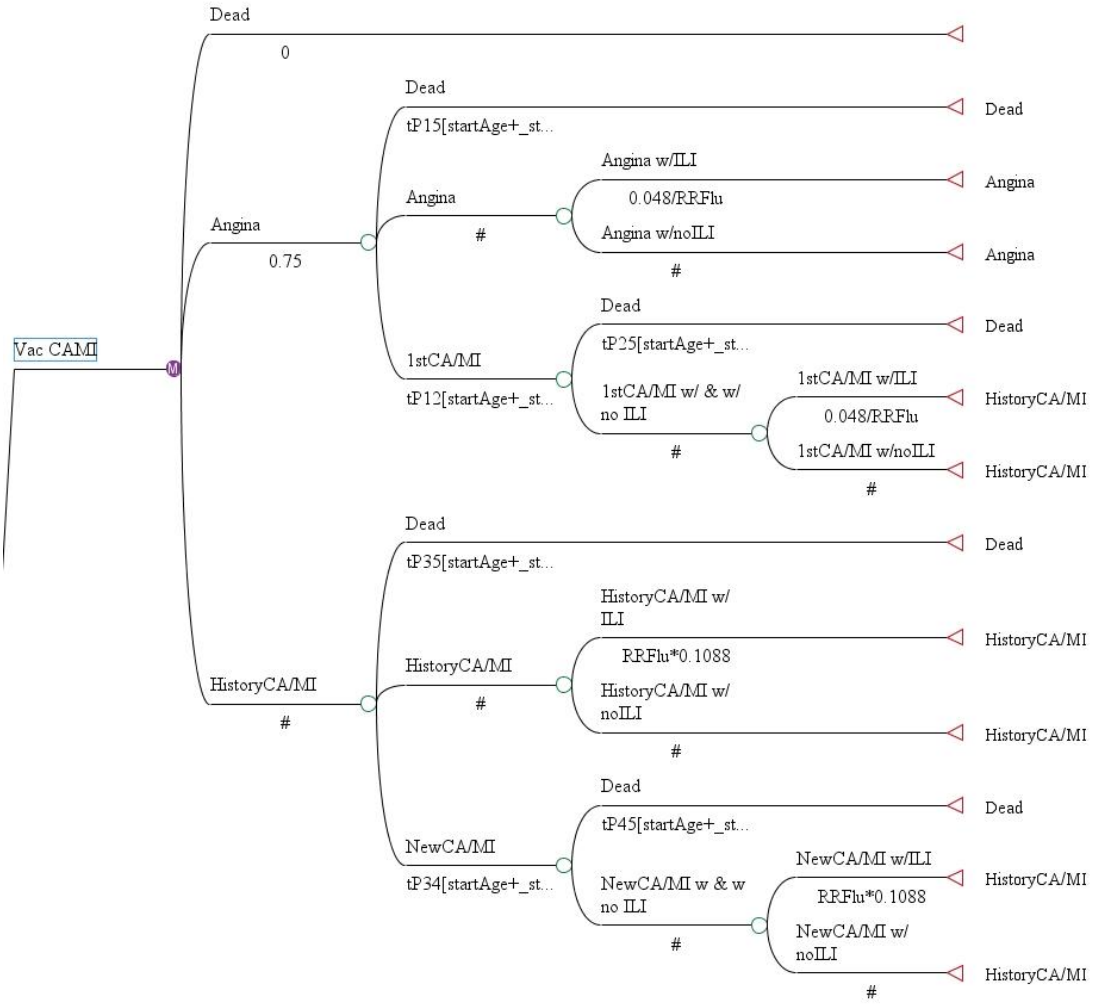
Subtree: Vaccination in Angina patients



APPENDIX D

Screenshots (Continue)

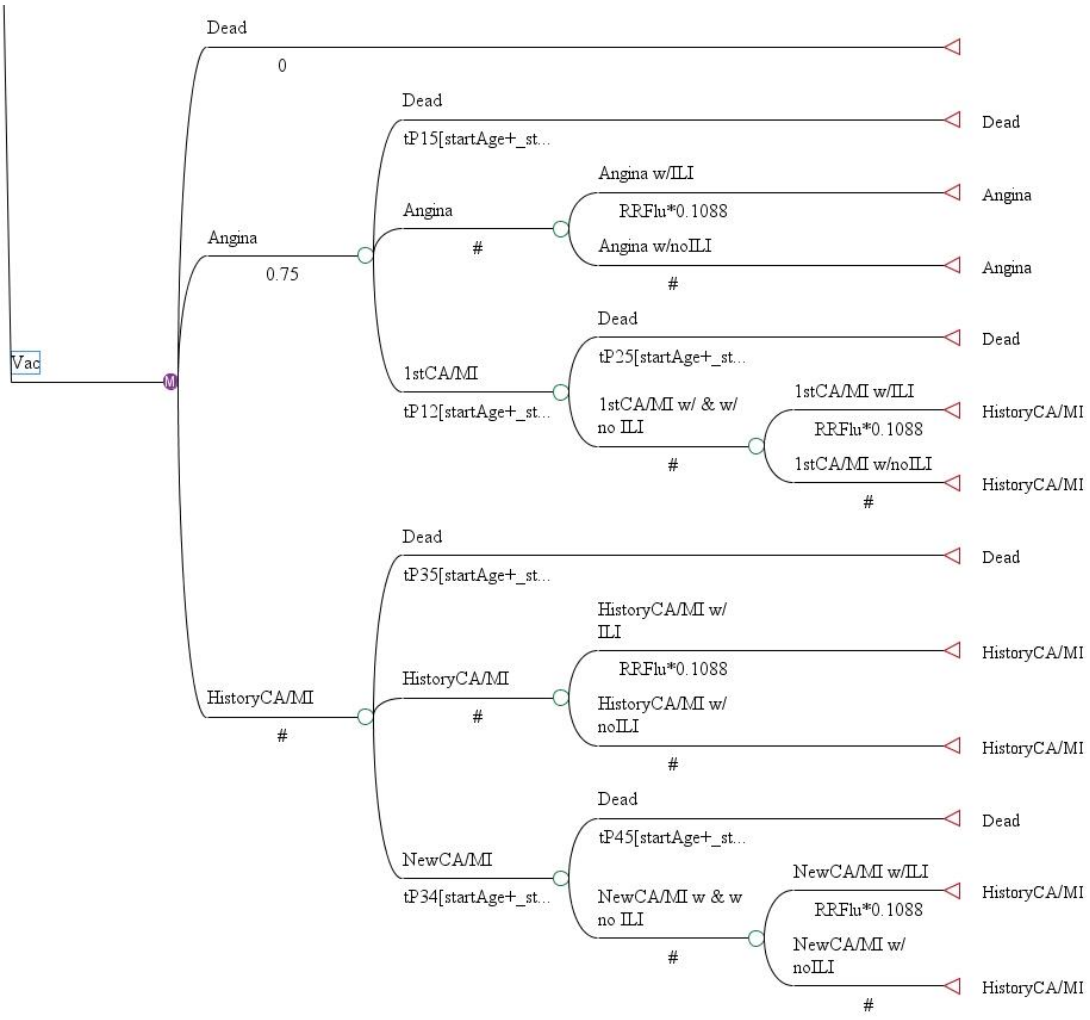
Subtree: Vaccination in CA/MI patients



APPENDIX D

Screenshots (Continue)

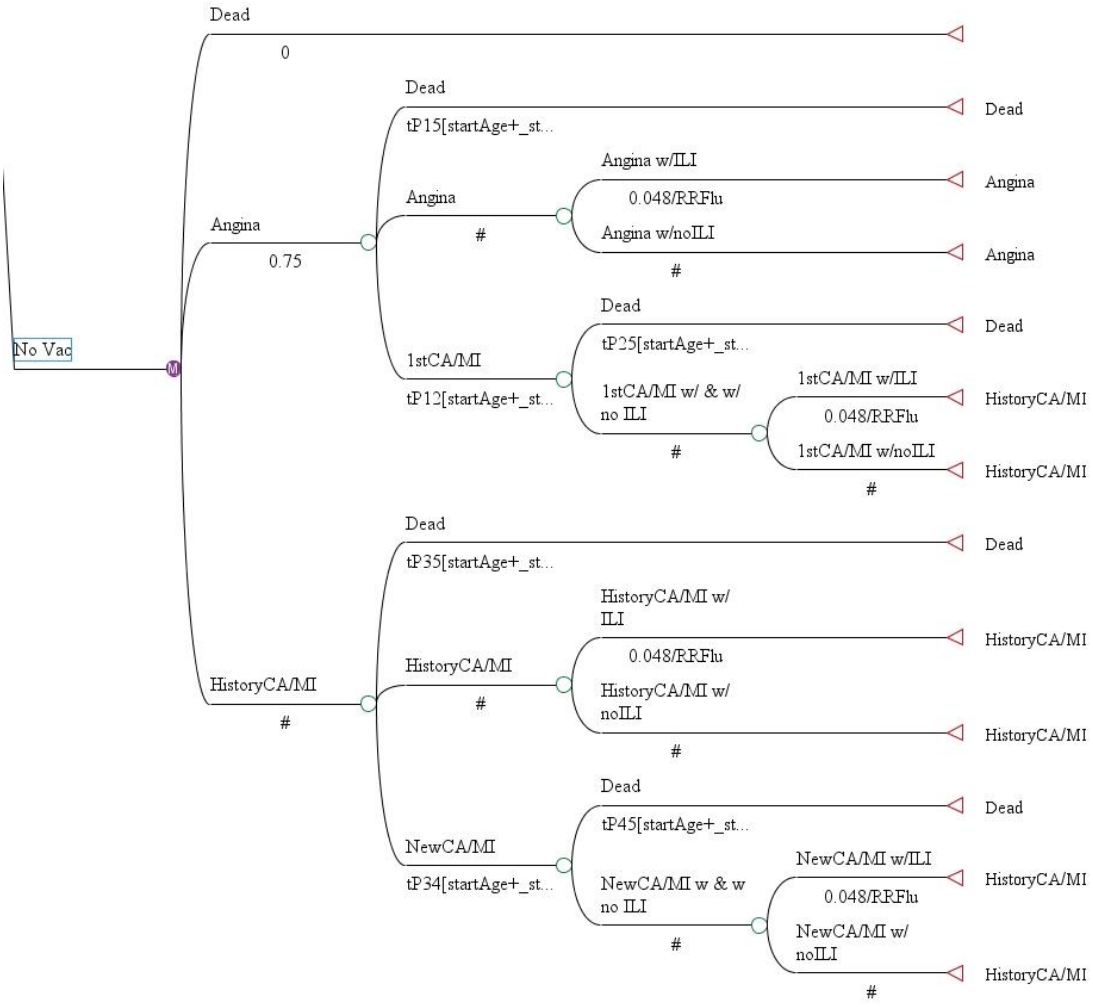
Subtree: Vaccination in CHD combined group strategy



APPENDIX D

Screenshots (Continue)

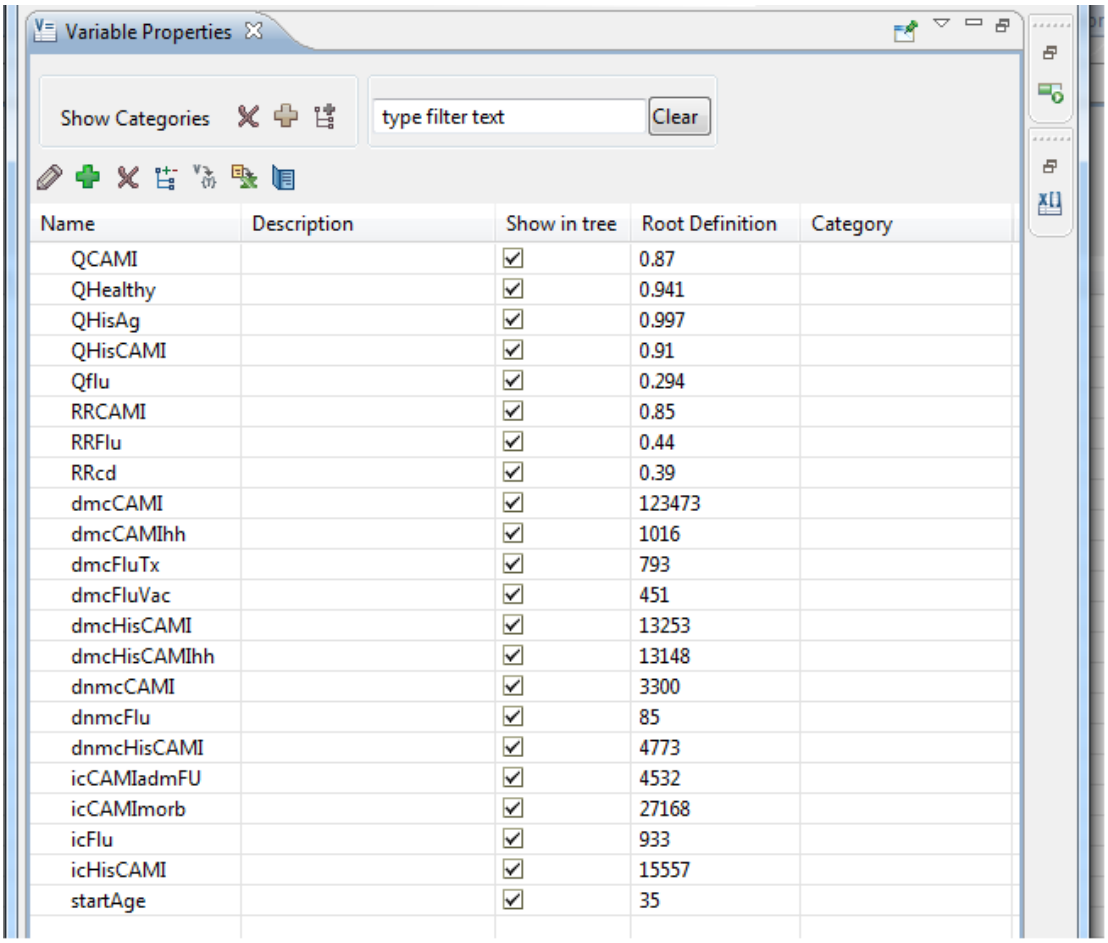
Subtree: No Vaccination strategy



APPENDIX D

Screenshots (Continue)

Variables Properties

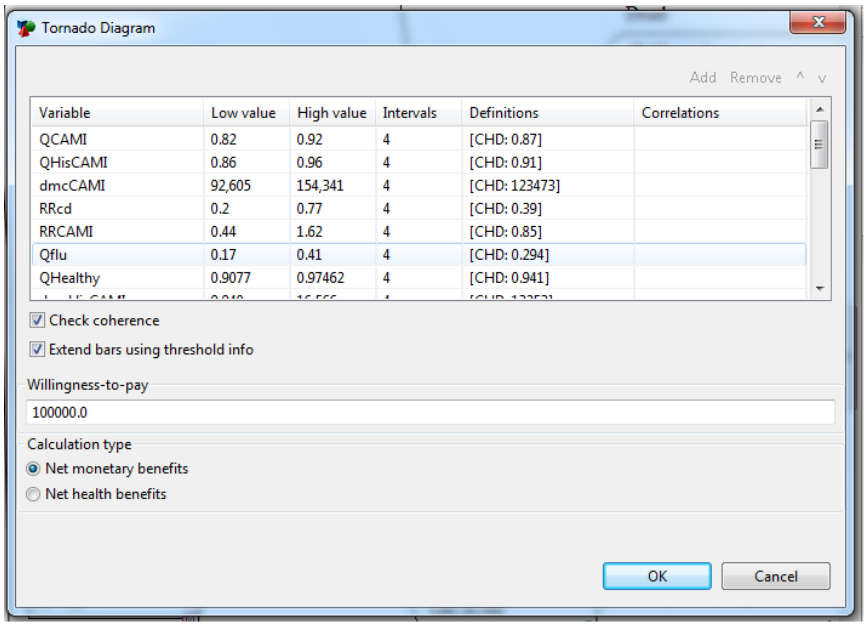


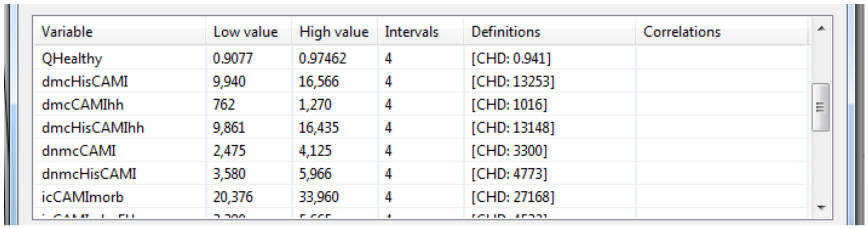
Name	Description	Show in tree	Root Definition	Category
QCAMI		☑	0.87	
QHealthy		☑	0.941	
QHisAg		☑	0.997	
QHisCAMI		☑	0.91	
Qflu		☑	0.294	
RRCAMI		☑	0.85	
RRFlu		☑	0.44	
RRcd		☑	0.39	
dmcCAMI		☑	123473	
dmcCAMIhh		☑	1016	
dmcFluTx		☑	793	
dmcFluVac		☑	451	
dmcHisCAMI		☑	13253	
dmcHisCAMIhh		☑	13148	
dnmcCAMI		☑	3300	
dnmcFlu		☑	85	
dnmcHisCAMI		☑	4773	
icCAMIadmFU		☑	4532	
icCAMImorb		☑	27168	
icFlu		☑	933	
icHisCAMI		☑	15557	
startAge		☑	35	

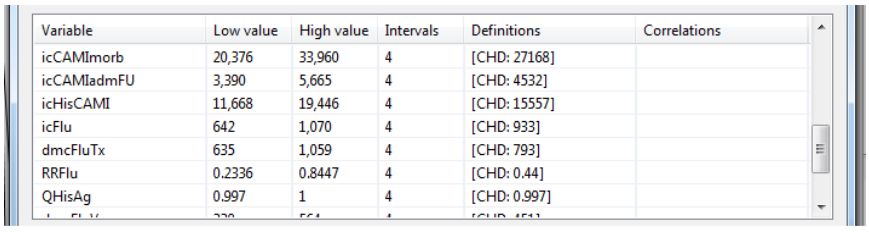
APPENDIX D

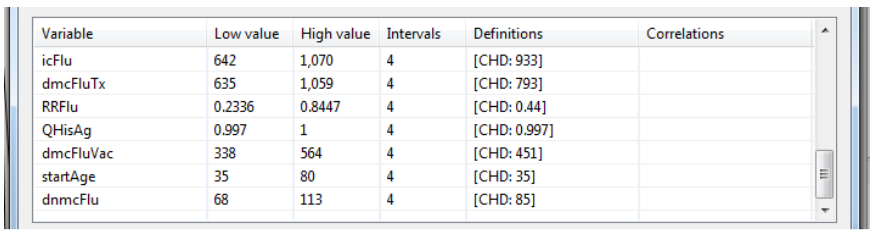
Screenshots (Continue)

Variable values entered for Tordano diagram





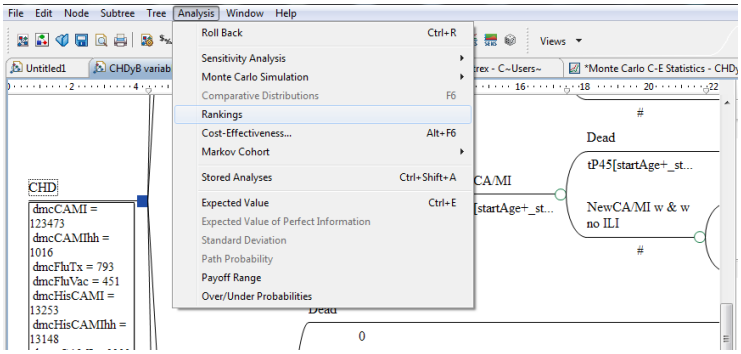


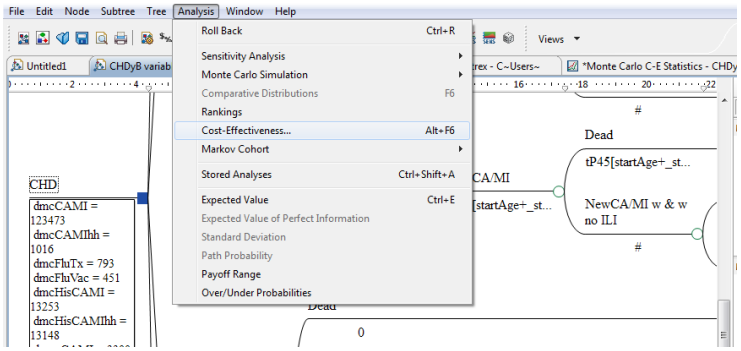


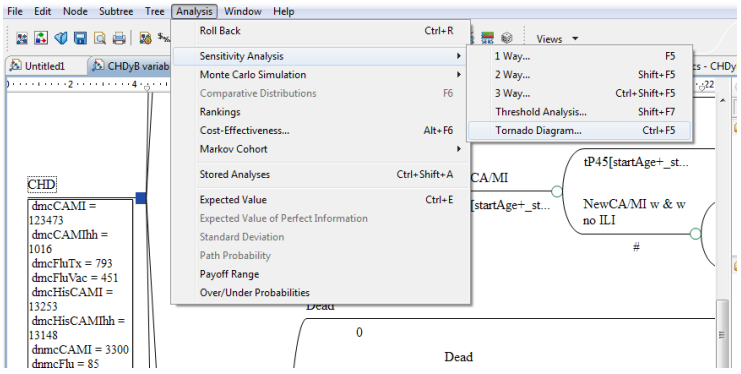
APPENDIX D

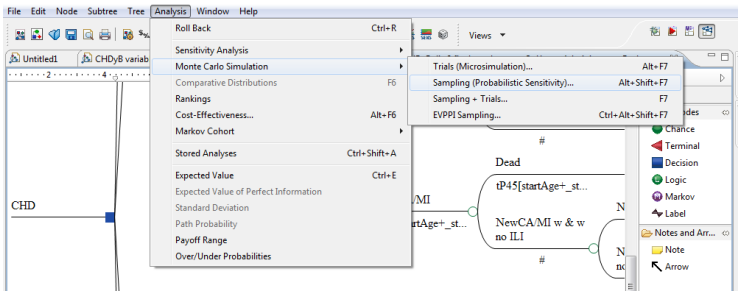
Screenshots (Continue)

Analyses









BIOGRAPHY

Mrs. Pongphaya Choosakulchart was born on November 6, 1966 in Bangkok, Thailand. She graduated from Faculty of Pharmacy, Mahidol University for Bachelor Degree of Sciences, Pharmacy in 1990. She was also graduated from Rangsit University for Master Degree of Business Administration in 2000. She was a Ph.D. candidate in Social and Administrative Pharmacy at Chulalongkorn University in 2012. She works as a consultant and representative for malaria research and other clinical research in South East Asia.