Cost-utility analysis of seasonal influenza vaccine among school children in Thailand

1. Background

1.1 Seasonal influenza

Influenza occurs in both pandemic and seasonal forms. Pandemics, defined as sustained spread of new influenza shift variants in at least two WHO regions, occur infrequently [1]. For example, there were three pandemics in the 20th century. Morbidity and mortality due to influenza are usually particularly high during the occasional global pandemic, though can also vary within a single pandemic. On the other hand, in the years between influenza pandemics, which are called interpandemic periods, influenza epidemics occur almost every year. We refer to this interpandemic influenza as “seasonal influenza” to distinguish it from pandemic influenza. Seasonal influenza is usually less severe in its impact compared to pandemic influenza, but can also show considerable between-year variation. Nonetheless, seasonal influenza has a substantial effect, particularly in vulnerable population groups, and cumulative mortality due to seasonal influenza is believed to greatly exceed that due to pandemic influenza [2].

In temperate and cold climates, the epidemiology of seasonal influenza is clearly characterized by the occurrence of one annual epidemic during the winter months (November-March in the Northern Hemisphere; June-September in the Southern Hemisphere) [2-3]. While there are limited published data on influenza in tropical and subtropical areas, it appears that the timing of periods of influenza epidemics is less distinct in these settings and more variable; seasonal influenza epidemics can sometimes occur twice a year or even throughout the year [4]. For example, in Thailand, during the years 1988-2008, influenza like illness (ILI) incidence was observed year-round, with two peaks per epidemic year: a smaller peak in January-March and a larger peak in June-September [5-6].

The recent pandemic in 2009 has raised awareness and concerns regarding preparedness and interventions against seasonal and pandemic influenza [7-8]. As our understanding of transmission dynamics and determinants of seasonality at a local scale (i.e. in the tropics) improves, there is the potential to develop better methods for the management and control of annual influenza epidemics, in particular through improved vaccination strategies against seasonal influenza.

1.2 Influenza Vaccine

Vaccination is at present the primary public health intervention for the reduction of illness caused by seasonal influenza, followed by antiviral drugs [9-11]. Vaccines protect against influenza by stimulating an antigen-specific immune response in recipients. To be effective at reducing influenza illness the antigens contained in the vaccine must match those of the circulating virus.

There are two types of influenza vaccines, live attenuated influenza vaccine (LAIV) and trivalent inactivated vaccine (TIV). LAIV is suggested for individuals aged 2 to 49 years while TIV is indicated for those aged 6 months and older [12]. A recent meta-analysis reported that the pooled efficacy for preventing laboratory-confirmed of LAIV versus placebo is 83% in children aged 6 months to 7 years and 59% in adults aged 18 to 65 years for TIV [13]. Another meta-analysis reported that year 1 efficacy of two doses of LAIV was 83% for those aged 2 to 17 years when compared to placebo and year 2 efficacy of LAIV was 87%for the same age group. This study estimated that those receiving LAIV had 44% (caused by similar strains) and 48% (caused by all strains) fewer cases of influenza than those receiving TIV [14]. One study estimated LAIV to have 82% efficacy and TIV to have 59% efficacy for healthy children aged 2 to 16 years [15]. This study also mentioned that there was a marked difference between vaccine efficacy and effectiveness (for preventing influenza like illness); the effectiveness for prevention of influenza-like illness is 33% and 36% for LAIV and TIV respectively. It seems that both vaccine types have moderate protection against seasonal influenza. All studies found that LAIV had higher efficacy than TIV. However, it should be

noted that we still have the substantial gaps in our knowledge about efficacy or effectiveness for some age groups [13].

Reported reactions or reactogenicity events (REs) to influenza vaccines include runny nose/nasal congestion, sore throat, cough, vomiting, headache, muscle aches, chills, decreased activity, irritability, decreased appetite, and fever. REs in vaccine-naïve children that were reported by significantly more frequent amongst LAIV recipients than placebo recipients were nasal congestion (58.1% vs. 49.6%), fever (16.1% vs. 11.2%), decreased activity (14.5% vs. 10.5%), and muscle aches (6.0% vs. 2.8%) for the first vaccine dose. Surprisingly, the frequency of cough in the LAIV group was lower than in the placebo group (29.7% vs. 34.1%). For the second dose, only nasal congestion and appetite decrease were significantly more frequent than in the placebo group. Compared with the first dose of TIV, the frequency of REs in the LAIV group were higher than in the TIV group only for nasal congestion (54.1% vs. 43.2%). Cough was still lower in LAIV group than it was in the TIV group (30.5% vs. 32.0%). There was no significant difference in REs between LAIV and TIV groups after the second-dose vaccination [16]. From medical record review among previously unvaccinated and TIV vaccinated children, increased frequency of gastrointestinal tract symptoms (incidence rate ratio (IRR), 1.18), gastrointestinal tract disorders (7.70), and fever (1.71) were significantly associated with vaccination [17].

1.3 The use of mathematical models in evaluating possible influenza vaccination control programme

Mechanistic mathematical models are used in many areas of the life sciences to study both within-host processes (e.g. pharmacokinetics and pharmacodynamics) and between-host processes (e.g. demographics and epidemics) .They are useful not only for developing an understanding of mechanisms generating observed outcomes and evaluating hypothetical scenarios, but also for highlighting what we know and, equally importantly, what we don't. Disease transmission models aim to simplify potentially complex systems into their

key processes and enable us to investigate how the different factors influence epidemic behaviour.

Conventional static models (i.e. models that do not account for how the force of infection evolves in time) fail to capture such indirect effects and consequently will have a tendency underestimate the benefit of vaccination programme. Instead non-linear dynamic epidemic models (which we refer to simply as mathematical models) are needed. To be of practical value such models must be adapted to both the pathogen of interest, the interventions we want to consider, to the demographics of the population we want to study, and local conditions such as seasonal factors. Overestimation of vaccine benefits is also possible in both static and dynamic models, for example if the effectiveness of vaccination is overestimated or the immunogenicity of naturally occurring infection is underestimated.

Again, dynamic mathematical models are required if we want to fully account for such herd immunity effects and to take advantage of them in designing more efficient vaccination programmes. Furthermore, vaccination programmes which are not able to eliminate a pathogen can profoundly alter the age distribution of incident cases. Typically, we find that because vaccination programmes reduce intensity of transmission the average age at which people become infected increases. Since the consequence of infection (risk of hospitalisation, death etc.) can vary greatly with the age of infection, this means that in some cases poorly-designed vaccination programmes can actually lead to worse outcomes at a population level even though the vaccine benefits those receiving it. Again, mathematical models provide valuable tools for assessing the likely effects of vaccination programmes on incidence of disease in different age groups and for assessing the chance of such adverse outcomes. There are a number of published dynamic models for both pandemic and seasonal influenza [11,18]. However, very little published work has addressed the dynamics of seasonal influenza in the tropics and no previous work has used such a dynamic modelling approach to evaluate the potential health and economic consequences and cost-effectiveness of seasonal influenza vaccination programmes in Thailand.

2. Objectives

2.1 General objectives

To assess the cost-utility of providing either live attenuated influenza vaccine (LAIV) or trivalent inactivated vaccine (TIV) for school-aged children to prevent seasonal influenza infection; and ii) provide information on the expected impact of seasonal influenza vaccination in Thailand to aid decision making amongst policy-makers.

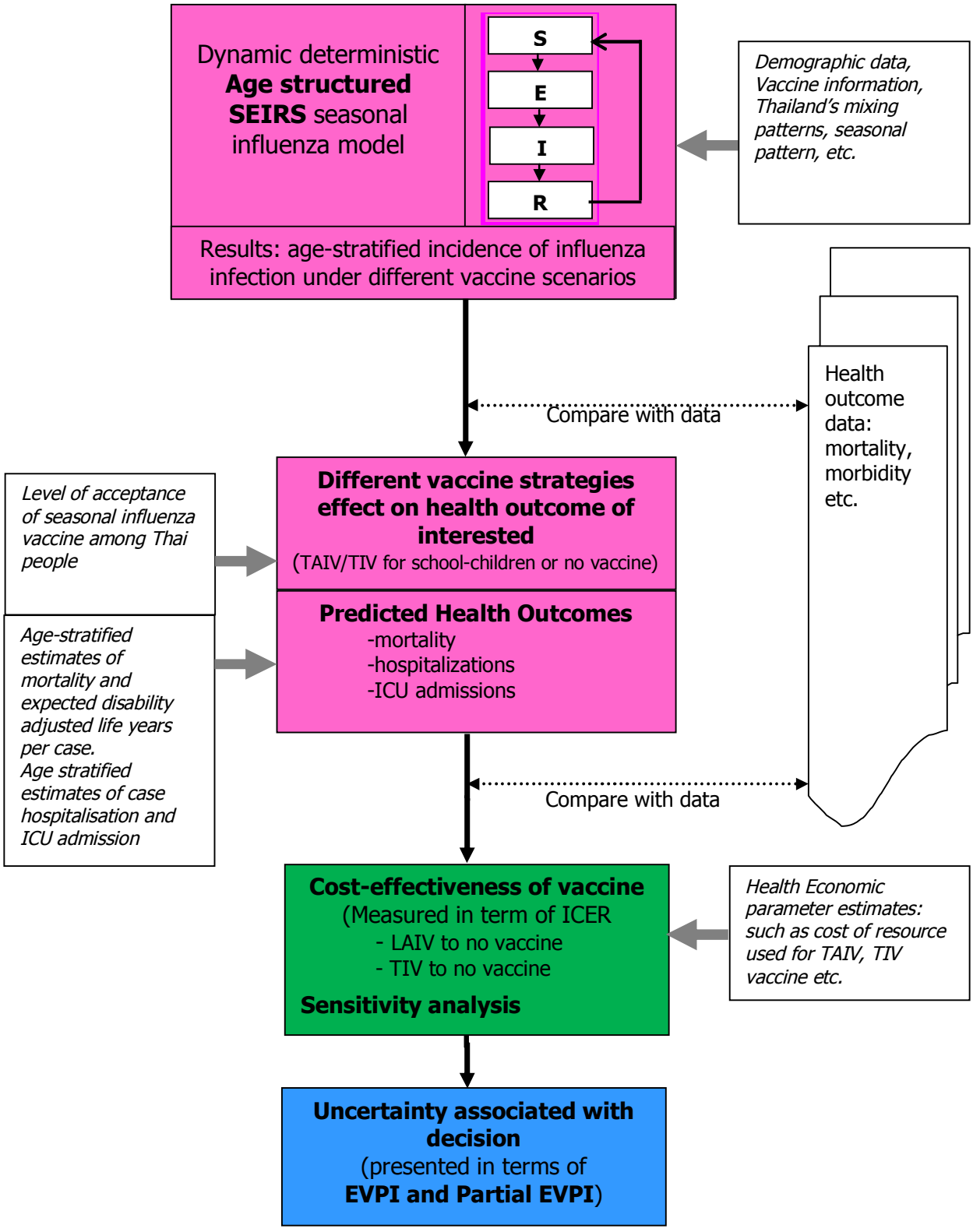
2.2 Specific objectives

1. To develop an age-structured mechanistic model for used for evaluating seasonal influenza vaccination policies in Thailand;
2. To identify resources used for providing either LAIV or TIV vaccine to school-aged children, ages 2-17 years, to prevent seasonal influenza infection in Thailand;
3. To estimate the costs and consequences of vaccinating school children, using either LAIV or TIV compared to no immunization, on the basis of existing evidence;
4. To identify priority areas for further research to be undertaken in the future in order to reduce level of uncertainty associated with the coverage decision.

3. Methodology

The work includes: 1) development of a dynamic epidemiological model that will be used to evaluate the impact of vaccination programme on age-stratified incidence of seasonal influenza infection under a variety of scenarios; 2) a model-based cost-utility analysis to estimate the incremental cost effectiveness ratios (ICERs) of providing either LAIV or TIV vaccination programme compared with no vaccination programme in school-aged children population, including a multivariate sensitivity analysis; 3) an expected value of perfect information (EVPI) analysis and a partial EVPI analysis to assess the degree to which decision-making could be improved by removing and reducing parameter uncertainty (Figure 1).

Figure 1. Modelling workflow.



Schematic diagram of the methodology and the information/data that are required for both the model-building stage (pink), the estimate of the costs and consequences of vaccinating school children using either LAIV or TIV compared to no immunization (green), and the partial EVPI (blue). SEIRs: Susceptible Exposed Infectious Recovered Susceptible. ICER: incremental cost-effectiveness ratio. EVPI: expected value of perfect information.

3.1 A dynamic mathematical model

The dynamic epidemiologic model will be used to obtain the age-stratified incidence of seasonal influenza infections under different vaccination programme scenarios. Figure 1 (pink box) shows the epidemiologic model that will be used for assessing costs and consequences of intervention options (vaccination and no vaccination programme). The age-structured deterministic mathematical transmission dynamic model will be based on a SEIRS structure, meaning that the whole Thai population divides into four compartments representing different disease states: susceptible (S) representing those who have not been infected or successfully vaccinated and are therefore fully vulnerable to infection together with those who have been vaccinated but who have since lost immunity against circulating influenza subtypes due to antigenic drift; exposed (E) representing those who have been infected, but who have not yet progressed to become infectious (i.e. able to infect others); infectious (I) (i.e. infected and able to infect others); and recovered (R) representing the people who are no longer vulnerable to infection with the same virus type, either because they have been infected and recovered, developing immunity, or because they have been effectively vaccinated. The model will account for age and risk group-structured transmission and also account for seasonal forcing patterns for influenza transmission in Thailand. The model will be calibrated using influenza data from Thailand [19-22]. This will ensure that the model predictions are based on real data concerning the influenza-related health outcomes of interest (age-stratified mortality, hospitalizations, and ICU admissions). Model fitting will be carried out within a Bayesian framework, using priors for model parameters derived from both literature review and formal elicitation of expert opinion [23]. Fitting the model to data will yield a joint posterior distribution for model parameters. This joint posterior distribution will quantify knowledge and uncertainty about parameters which will be accounted for when analyzing the impact of the vacation programmes. In the event that a full Bayesian analysis cannot be completed within the allotted timeline, alternative less computationally expensive fitting techniques will be employed, such as those employed previously in other influenza modeling studies [18, 24].

3.1.1 Model structure

By using ordinary differential equations, we can consider the events occurring at continuous time rather than in discrete time interval. The mathematical model of each of the four compartments can be described below.

$$\frac{dS_i(t)}{dt} = b(1-v)N_i(t) - \lambda_i(t)S_i(t) + \rho S_i(t) - mS_i(t)$$

$$\frac{dE_i(t)}{dt} = \lambda_i(t)S_i(t) - f_iE_i(t) - mE_i(t)$$

$$\frac{dI_i(t)}{dt} = f_iE_i(t) - rI_i(t) - mI_i(t)$$

$$\frac{dR_i(t)}{dt} = bvN_i(t) + rI_i(t) - mR_i(t) - \rho R_i(t)$$

$$N_i(t) = S_i(t) + E_i(t) + I_i(t) + R_i(t)$$

Where, *i* corresponds to the age group (one-year age band) and includes all age groups (not just school-aged children).

$\frac{dS(t)}{dt}$ denotes the rate of change in the number of susceptible individuals at time t.

$\frac{dE(t)}{dt}$ denotes the rate of change in the number of exposed individuals at time t.

$\frac{dI(t)}{dt}$ denotes the rate of change in the number of infectious individuals at time t.

$\frac{dR(t)}{dt}$ denotes the rate of change in the number of recovered (immune) individuals at time t.

$S(t), E(t), I(t), R(t)$ equal the total number of individuals who are susceptible, exposed, infectious and immune/recovery respectively at time t.

$N(t)$is the total population size at time t.

f denotes the rate of onset of infectiousness.

r denotes the rate at which individuals recover from being infectious.

$\lambda_{i(t)}$ denotes the force of infection in age group *i* at time t. This will depend on the number of infectious individuals in this and other age groups and patterns of mixing between the age groups which will be taken from a previously performed contact survey in Thailand.

m denotes the mortality rate.

v_i is the introduction of vaccination for a proportion of people in age group *i*.

ρ is a proportion of immunity waning due to different sub-type of virus introduced.

For notational convenience, aging has been neglected in the above equations. This will be accounted for by using one year age bands and shifting each person to the next age band at the end of each year. In practice, it may be challenging to estimate a realistic value for the rate of waning of immunity, ρ. In the base case analysis we will assume conservatively that there is no lasting immunity between different years and fit the model to individual years separately. Given that the long-term effects of vaccine-induced immunity and immunity from natural infections are poorly understood, we will also perform sensitivity analyses where we consider alternative plausible scenarios.

3.2 Modelling Cost-Effectiveness

Health-economic evaluation uses decision analytic models to predict outcomes in terms of costs and health benefits [25]. A baseline model will describe the costs and health outcomes associated with providing either the LAIV or TIV vaccination programme compared with no vaccination programme (Figure 1, green box). Cost, effectiveness, and utility parameters will be put into the model to estimate the total cost and health gained from each

option. Health benefits will be expressed in terms of disability adjusted life years (DALYs) averted. The influenza-related or influenza-liked disability weights will be obtained from local studies via the Health Technology Assessment Database [26]. If there are more than one studies identified, meta-analysis will be employed in order to combined the quantitative data. In case of no relevant disability weights available in Thailand, researchers will perform a comprehensive literature review for obtaining those values from other settings. The study adopts one-year time horizon in base-case analysis. All costs and cost-utility ratios will be reported based in year 2012. In addition, given that the long-term effects of vaccine-induced immunity will be examined through sensitivity analysis, 3% discounting rate as suggested in the national methodological guideline for conducting health economic evaluation will be applied for costs and outcomes obtained beyond based year (2012).

The results in terms of value for money will initially be presented in term of an incremental cost-effectiveness ratio (ICER) where:

$$\text{ICER} = \frac{\text{Cost of vaccination programme} - \text{Cost of current practice}}{\text{Outcome of vaccination programme} - \text{Outcome of current practice}}$$

The ratio is often interpreted in light of a decision-maker's maximum willingness to pay for a unit of health outcome. Programmes might be considered cost-effective if they generate an incremental cost-effectiveness ratio (ICER) that is less than the willingness to pay. The Subcommittee for Development of the National List of Essential Medicines and the Subcommittee for Development of the Health Benefit Package and Service Delivery of the National Health Security Office recommend that health intervention yielding equal or less than one capita gross domestic product (GDP; US$4,800 in 2011) per DALY averted represents good value for money (cost-effective) under the Thai healthcare setting [27]. However, in some circumstances, especially vaccine introduction, the zero threshold (0 Baht/DALY averted) is referred in Thailand [28]. Thus, this study will use both thresholds in the analysis.

The study will be conducted using costs not only incurred from the health system perspective (direct medical costs only) but also from the societal perspective (accounting for direct medical, direct non-medical, and indirect costs) since considering only the costs from the hospital might underestimate the total costs of treatment for the influenza infections. Direct medical costs will be identified from hospital database including all out-patients and in-patients cares provided in both public and private health facilities. Direct non-medical costs, including costs of transportation, foods and lodging, and indirect costs, such as productivity loss of patient from work absenteeism, will be retrieved from local studies.

Infection with seasonal influenza can occur with varying levels of severity, and the risk of severe cases is known to vary according to the age group. Based on uncertainty of parameters, a series of one-way sensitivity analysis will be performed in order to identify the most sensitive parameters amongst key parameters and assumptions, such as vaccine efficacy, severity of infection, annual risk of infection reduction, vaccine costs, that affect this economic evaluation analysis. Moreover, discount rate of 0 – 6% will be used to observe any changes in the conclusion of results as recommended in the Thai health technology assessment guideline [29]. A full multi-parameter sensitivity analysis will also be performed using a Monte Carlo approach. This approach repeats the analysis many hundreds of times with different model parameters. To reflect uncertainty in true value of the parameters this will be done by sampling parameters from their joint posterior distribution. Results will be expressed as cost-effectiveness acceptability curves (CEACs).

3.3 Expected value of perfect information (EVPI) and Partial EVPI

Because we do not know the model parameters with certainty, and because the best policy depends on the values of these parameters, there is a chance that we will not choose the best policy. EVPI tells how much we would benefit if we knew all parameters perfectly and therefore had no chance of failing to choose the optimum policy. Meanwhile, a partial EVPI tells how much we would benefit if we knew key uncertain parameters.

The EVPI reflects the uncertainty as to which decision achieves the lowest ICER. If we had perfect information, we would always be able to choose the policy with the lowest ICER. However, because of imperfect information, choosing the policy that minimises the expected ICER we will sometimes select a suboptimal policy.

The EVPI is defined as:

$$EVPI = E_\theta\left[max_j\{B(j,\theta)\}\right] - max_j\{E_\theta[B(j,\theta)]\}$$

Here θ represents the model parameters (which are uncertain, though we assume we know their joint distribution), j is the policy option, and B(j, θ) is the net benefit for policy j with parameters θ. The net benefit is the different between the monetary value of the health gains (i.e. the willingness to pay per DALYs averted multiplied by the number of DALYs averted) and the net cost of the intervention.

The second term on the right hand side is the expected net benefit of the best policy. To estimate this we sample a large number of parameters θ from their posterior distribution (which reflects everything we know or believe about these parameters). Suppose we sample N parameter sets (where N might be 10,000 or 100,000 or more). Call these samples $\theta_1 \ldots \theta_N$. For each sample θ_i we run the model to evaluate the net benefit for each policy, j. For each sample and each policy we use these simulations to calculate the expected incremental net benefit $B(j,\theta)$. Then we obtain the overall expected net benefit of each policy, j, by averaging over these N values. The right hand side is then just the maximum for these expected net benefits. This represents the net benefit of the best policy we can choose given what we currently know about the parameters θ.

Assuming we store all these simulation results, we can calculate the first term on the right hand side, the expected net benefit given perfect information, without performing any more simulations. All we need to do is to look at the stored values, $B(j,\theta)$, and for each sample to choose the largest value. That is, for each sample we select the best policy j.

The partial EVPI (or pEVPI) is defined as:

$$pEVPI(\theta i) = E_{\theta i}\left[max_j | E_{\theta c|\theta i}\{B(j,\theta)\}\right] - max_j\{E_\theta[B(j,\theta)]\}$$

Here θ divided into two subsets, θ_i and its complement θ_c ,and we wish to know the expected value of perfect information about θ_i (which are key parameters). The pEVPI is necessarily less than the overall EVPI.

4. Data collection

We will utilize the estimations of the efficacy of the vaccine from a literature reviews and expert opinions. The other information will be based on literature review (Table 1). Costs consist of direct medical costs, direct non-medical costs and indirect costs considered from the societal perspective.

Table 1 Data used in the model and their sources

Parameter	Source
Epidemiology	
Probability of seasonal influenza infection	Literature reviews
Probability of hospitalization due to influenza	Literature reviews
Probability of ICU admission due to influenza	Literature reviews
Probability of adverse events from vaccination	Literature reviews
Probability of death due to influenza	Literature reviews
Mixing patterns between different age group in Thailand	Thailand contact survey
Mortality/Morbidity	
Baseline mortality of Thai population	Burden of disease project
Mortality/Morbidity rate of seasonal influenza infected patients	Literature reviews
Intervention effect	

Parameter	Source
Efficacy and safety of LAIV and TIV vaccine	Literature reviews
Vaccine acceptance	
Acceptance of seasonal influenza vaccine among Thai people	Literature review
Acceptance of seasonal influenza vaccine	Literature reviews
Costs	
Cost per non hospitalized influenza-infected patients	Literature reviews
Cost per hospitalized influenza-infected patients	Literature reviews
Cost per ICU admissions influenza-infected patients	Literature reviews
Cost of adverse events management per patient	Literature reviews
Cost of LAIV and TIV vaccine	Thai GPO*
Cost of logistics for vaccine delivery	Literature reviews
Direct non-medical and indirect cost (only for societal perspective)	
Cost per non hospitalize influenza-infected patients	Literature reviews
Cost per hospitalize influenza-infected patients	Literature reviews
Cost per ICU admissions influenza-infected patients	Literature reviews
Cost per vaccination	Literature reviews
Cost of adverse events management per patients	Literature reviews
Outcomes	
Disability of influenza infection	Literature reviews
Disability of hospitalization due to influenza	Literature reviews
Disability of ICU admission due to influenza	Literature reviews

**GPO: The Government Pharmaceutical Organization of Thailand which is responsible for producing and merchandising influenza vaccines*

5. Timeline

Project Activities	Time Frame (Month; start from July 2012)						
	1	2	3	4	5	6	7**
Literature review	←	—	→				
Consultation meetings with key experts in the field		←	→				
Parameterizing influenza transmission dynamic model	←	—	—	—	→		
Conducting economic evaluation analysis				←	—	→	
Organizing an expert meeting for considering of the preliminary results					←	→	
Report writing						←	→
Producing and disseminating reports							← →

** *The end of January 2012*

6. Research team and Budget

6.1 List of researchers

- **Dr. Aronrag Meeyai, Ph.D.** **Principal investigator**
- **Dr. Yot Teerawattananon, Ph.D.** **Researcher**
- **Dr. Naiyana Praditsitthikorn, Ph.D.** **Researcher**
- **Dr. Ben Cooper, Ph.D.** **Researcher**
- **Mr. Surachai Kotirum, Pharm.D.** **Researcher**
- **Ms. Warinya Deepana, Pharm.D.** **Research assistant**

6.2 Budget Details

6.2.1 Personnel

Budget justification	Day(s)	Rate (USD)	Sum
Principal investigator			
Role:			
1. Project supervision	200	40	
2. Literature review	90	40	
3. Data collection	30	40	
4. Parameterizing Influenza transmission dynamic model	90	40	
5. Economic evaluation analysis	60	40	
6. Writing and editing report	60	40	**21,200**
Researchers			
Role:			
1. Literature review	90	30 x 4	
2. Data collection	60	30 x 4	
3. Parameterizing influenza transmission dynamic model	60	30 x 4	
4. Economic evaluation analysis	30	30 x 4	
5. Writing report	60	30 x 4	**36,000**

Research assistant **Role:**			
1. Literature review	90	30	
2. Data collection	60	30	
3. Conducting and coordinating for expert meetings	60	30	
4. Writing meeting minute and report	60	30	**8,100**
Total budget required (round), USD	**65,000**		

6.2.2 Equipment

Category	**Quantity**	**Unit Cost**	**Total, USD**
Berkeley Madonna license fee	1	300	300
Total			**300**

6.2.3 Meeting

Category	**Quantity**	**Unit Cost**	**Total, USD**
Expert consultation meeting	2	200	400
Total			**400**

6.2.4 Documents/Printing

Category	**Quantity**	**Unit Cost**	**Total, USD**
Preliminary report	10	10	100
Final report	500	10	5,000
Publication fee for journal articles			5,000
Total			**10,100**

Grand Total	**75,800**

7. Utilization of Results

Most of the literature review, data collection, analysis work, writing and production of the report will be performed by the research team under close supervision of a national expert panel consisting of policy makers, vaccine experts, health professionals, academics, and representatives from civil society.

With the ever-increasing utilization of economic evaluation data for evidence-based decision making, this research will help to inform policy-makers in Thai healthcare sector, especially the National Vaccine Committee and the Subcommittee for Development of Benefit Package and Service Delivery under the Universal Coverage Scheme, about whether it is worthwhile to provide either LAIV or TIV influenza vaccine in a national vaccination programme for a given vaccine cost. HITAP is working closely with these two national authorities in development of new vaccines and health technologies, respectively. The results of this project will be also disseminated through other stakeholders, e.g. health professionals, academics, and general public. English and Thai reports of this study will also be available in public domain and there will be series of articles published in peer-reviewed journals alongside the model structure and program code.

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