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Does Thailand Need Its Own Mathematical Model of the Influenza A (H1N1-2009) Pandemic and the Following Seasonal Influenza?

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ABSTRACT

There are a number of mathematical modelling studies that consider optimum pandemic influenza vaccine allocation strategies and the potential impact of different vaccination strategies for seasonal influenza in affluent and/or temperate countries. The evaluation of these vaccination policies through mathematical models before their implementation is important because it helps to ensure the most efficient allocation of resources in order to minimize influenza burden. However, there have been no published mathematical modelling studies about vaccine strategies taking into account the fact that many countries are likely to only have limited vaccine supplies even in the long-term (i.e. lower and middle income countries). Moreover, none of these modelling studies have taken into account the pattern of seasonality of influenza transmission in the tropics. Because of these and other factors, there is a need to evaluate influenza vaccination strategies in light of the unique conditions faced in Thailand. This article also presents a framework for mathematical model development for pandemic and seasonal influenza in Thailand.

Key words: mathematical model, pandemic, influenza, seasonal influenza, vaccine

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Introduction

Influenza occurs in both pandemic and seasonal forms. Pandemics, defined as sustained spread of new influenza shift variants in at least 2 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. However, the novel swine-origin influenza A (H1N1) identified in late April 2009 in Mexico appears to be an exception, with the best estimates of mortality and hospitalisation no higher than seen with seasonal influenza (and possibly lower)[2]. By late July 2009, the virus had caused only 816 confirmed deaths worldwide[3], and the best estimate of the proportion of symptomatic cases that died was 0.048% (95% credible interval, 0.026%-0.096%)[2]. On the other hand, influenza epidemics occur almost every year, following a regular seasonal pattern in temperate zones. 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[4].

The influenza A (H1N1-2009) pandemic and the following seasonal influenza in Thailand

Not long after the influenza A (H1N1) virus was identified in Mexico (late April 2009), Thailand faced the same virus (10 May 2009)[5]. In Thailand, this pandemic showed a pattern of two waves: the first wave from June to September 2009, and the second from December 2009 to March 2010[6]. Between June and September 2010, approaching the prime time of seasonal influenza in Thailand, an increase in cases of reported influenza occurred[6]. This was probably in part due to circulation of the new pandemic H1N1 influenza type.

From the very beginning of the influenza A (H1N1-2009) pandemic up until now, Thailand has been facing very different circumstances to those in Europe and North America. During the early stages of the pandemic, Thailand had very limited doses of antiviral drugs. This contrasts with the substantial stockpiles of antiviral drugs that are held in parts of Europe and North America. Therefore, during the beginning of the pandemic Thailand used school closure, hand hygiene, and very limited antiviral drug policies to attempt control of the disease. There were no vaccines during the early stages of the pandemic, since development and production of vaccine against a specific type of influenza virus requires several months. However, vaccination is still the primary public health intervention for the reduction of seasonal influenza.

The first lot of trivalent inactivated influenza vaccine (TIV) that Thailand had was only 1 million doses, delivered at week 3, December 2009 (after the end of the first wave)

and the second lot, which was about 1 million doses, arrived in the second week of January 2010. Immunisation using these vaccines started on 11 January 2010 and finished in May[7]. Later there was an offer from the US to donate their unused vaccine. This was available because there was no longer significant influenza A (H1N1) activity in the US at the time of the offer and there were another six months until the usual US seasonal epidemic. This seasonal epidemic was considered likely to be caused by a drift variant of the current virus strain and therefore less easy to protect against using the current vaccine. The arrival of all lots of vaccine in Thailand occurred too late for use of the vaccine to make a major impact on the control of the influenza A (H1N1-2009) pandemic. Moreover, the total amount of the vaccine was far below the level needed to have a significant effect on the transmission dynamics (to achieve herd immunity, which provides population-level protection against pathogen invasion even amongst the unvaccinated, the vaccine coverage would have to be at least 60-70% of the total population[8,9]). Thailand attempted to solve the problem of obtaining sufficient vaccine by agreeing to manufacture the trivalent live attenuated influenza vaccine (TAIV) in 2009. However, it will take two to three years to make certain that these TAIV vaccines are safe. Eventually, Thailand should be able to produce enough influenza vaccine for the Thai population at a reasonable price. This would enable Thailand to cope with both future pandemics and seasonal influenza and might provide sufficient vaccine to support neighbouring countries as well.

Mathematical model of influenza

To construct a mathematical model for influenza is to reproduce, using equations, the transmission pattern of influenza within the targeted population. The transmission pattern has to be based on key characteristics of influenza (latent period, transmission method and seasonal variation in transmission, patient recovery rates, etc.) and on the population's age profile and behavioral patterns (contact rates within and between age groups).

The most natural mathematical transmission dynamic model for influenza is based on a deterministic SEIR 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 vaccinated and are therefore fully vulnerable to infection, 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), 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, developed immunity, or because they have been effectively vaccinated. Then a deterministic compartmental model can be set up using differential equations, which specify the rates of change in

the number of individuals in different disease compartments over time (Figure 1). In the simplest form, the parameters are 1) the rate at which susceptible individuals become infected (β), 2) the rate at which pre-infectious individuals become infectious (λ), and 3) the rate at which infectious individuals recover (γ). Then the model parameterization can be achieved by fitting a model to observed data.

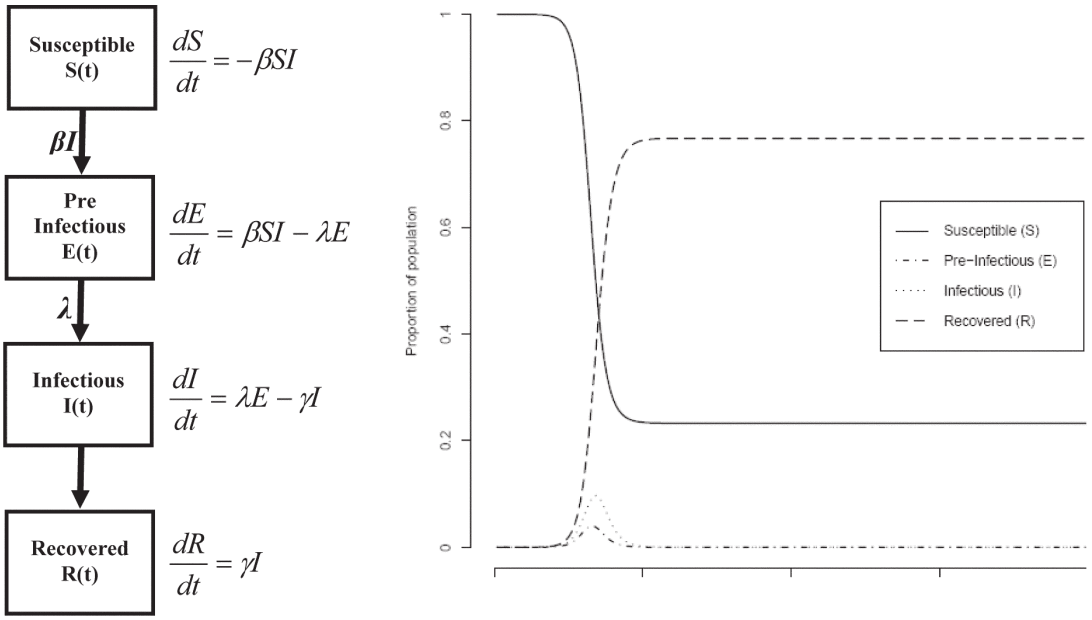


Figure 1 Schematic of SEIR model: a pictorial representation of the flow of individuals between compartments in the model; the differential equations which give the rate of change of the proportion in each compartment (positive values reflect flows into a compartment, whereas negative values reflect flows out of the compartment); and plot of numerical solution to the SEIR model, showing how the proportion of susceptible, pre-infectious, infected and recovered individuals in the population is predicted to change over time (modified from SIR model in[10]).

Mathematical models represent a valuable approach to evaluating the potential impact of public health intervention strategies for infectious diseases (under various prescribed assumptions) and informing policy decision making. Applied to influenza such mathematical models can help describe the epidemiological status of the population (estimating the number of people who are susceptible, infected and immune to a given strain), estimate transmissibility of the virus and the potential impact of public health responses (e.g. vaccinations, use of antivirals for treatment and prophylaxis, and school closure).

Mathematical models of pandemic and seasonal influenza in developed countries

There are a number of mathematical modeling studies that consider optimum pandemic influenza vaccine allocation strategies and the potential impact of different vaccination strategies for seasonal influenza in affluent and/or temperate countries[8-9,11-14]. The evaluation of these vaccination policies through mathematical models before their implementation is important because it helps to ensure the most efficient allocation of resources in order to minimize the burden of disease due to influenza.

Basta and co-workers used a stochastic simulation model of influenza transmission to consider strategies for vaccinating children to reduce overall population-level influenza attack rates in the US[13]. As expected, they found that the higher the vaccine coverage in children, the greater the reduction in the overall attack rate in other age groups. Interestingly, they reported that population-wide benefits of vaccinating children were strongest when transmission intensity was low to intermediate (when the reproductive number R, which represents the average number of secondary cases produced by a typical primary case, ranged from 1.2 to 1.6). Medlock and Galvani used a model parameterized with survey-based contact data and mortality data from influenza pandemics to determine optimal vaccine allocation in the US[14]. Their model recommended that optimal influenza vaccine distribution would be achieved by prioritization of schoolchildren and adults aged 30 to 39 years. Medlock and Galvani's work also showed that their recommendation was likely to lead to higher benefit than the vaccination recommendations from the CDC for influenza A (H1N1-2009) (by prioritizing young people aged 6 months to 25 years), and for seasonal influenza (by vaccinating children aged 6 months to 18 years and adults aged 50 and over) for all outcome measures (deaths, infectious, year of life lost, contingent valuation, and economic costs). Baguelin et al. adapted an SEIR model to include both different age groups and different risk groups and adopted a deterministic modelling framework to predict the impact of vaccination on the 2009 pandemic in England and Wales and evaluate the cost-effectiveness of this intervention[15]. Their analysis made use of seroprevalence data which confirmed that a significant fraction of individuals had been infected in the first wave of the epidemic and could therefore be considered immune. As the risk of serious consequences following infection is much higher in the high risk groups (i.e. those who are immunosuppressed or who have diabetes or chronic respiratory, heart, kidney, liver, or neurological disease), Baguelin's model assumed that vaccinating these groups is likely to be more effective at reducing deaths than vaccinating low risk individuals. Overall, they found that vaccination of the high-risk groups would prevent about 45 deaths (80% credibility interval 26-67) from about 250 (approximate 80% credibility interval 150-400), and would have saved around 2900 QALYs (80% credibility

interval 1600-4500). However, they reported that the effect of extending vaccination to include those not in high risk groups (i.e. to school-age children and the elderly) is highly dependent on the early availability of vaccines during the pandemic. Tuite et al. used a deterministic age-structured model of influenza to investigate the optimal pandemic influenza vaccine allocation strategies in the Canadian population[9]. They found that in the pandemic period vaccine should be allocated to high-risk groups, regardless of age, followed by age groups at increased risk of severe outcomes rather than targeting specific age groups for their population-wide effects. Vynnycky and co-workers focused on the impact of childhood influenza vaccination programs in England and Wales on seasonal influenza using an age-structured transmission dynamics model[16]. They reported that the long-term incidence of influenza A could decrease by 11-21% in the overall population by vaccinating individuals aged 6 months to < 2 years, and by 22-38% and 65-97% through targeting those aged 6 months to < 5 years and 6 months to 16 years, respectively.

Mathematical models of pandemic and seasonal influenza in Thailand

Until Thailand can produce vaccine in large quantities or vaccine manufactured elsewhere can be bought at a much lower cost, achieving sufficient vaccine coverage to generate herd immunity is an unrealistic goal. While optimal vaccination strategies with very low levels of vaccine are almost certainly those that target the highest risk groups, as vaccine supplies increase above the level needed to cover the high risk groups, optimal allocation of remaining vaccine among the rest of the population becomes increasingly important.

Questions such as "Who should we vaccinate (with the remaining vaccine) in order to minimize mortality, hospitalizations and ICU admissions and maximise quality adjusted life years?" need an answer. There are also a number of new questions specific to or with particular relevance for Thailand. For example: what policy should we use for a possible third wave (or the following seasonal influenza which is most likely in part due to circulation of a variant of the new pandemic H1N1 influenza type)? What should Thailand's long-term policy for future pandemic and seasonal influenza be, once Thailand is able to produce its own TAIV (i.e. how much TIV should Thailand continue to buy,-and how much TAIV should Thailand produce)? What will be the best policy during the transient period when Thailand can supply some intermediate level of TAIV?

So far, there has been no publication of a mathematical modelling study about vaccine strategies in lower and middle income countries, taking into account the possibility that some countries may be likely to only have limited vaccine supplies (such as Thailand). Answers to the above questions would help decision-makers in the development of evidence-based policy. A mathematical model that can be used for evaluating the direct and indirect effects of influenza vaccination strategies on all health outcomes that we are interested in to mitigate and

control pandemic and seasonal influenza in Thailand is essential.

Potential mathematical model of pandemic and seasonal influenza in Thailand

When building mathematical models to evaluate vaccination policies an important question arises: what level of complexity do the models need to have? A general principle is that models should be as simple as possible for addressing the questions of interest, but no simpler. As model complexity increases above a certain level, predictive performance of the model actually decreases (surprisingly simple models have been shown to have the best predictive power), and models become harder to understand, harder to verify, and harder to fit to data as complexity increases.

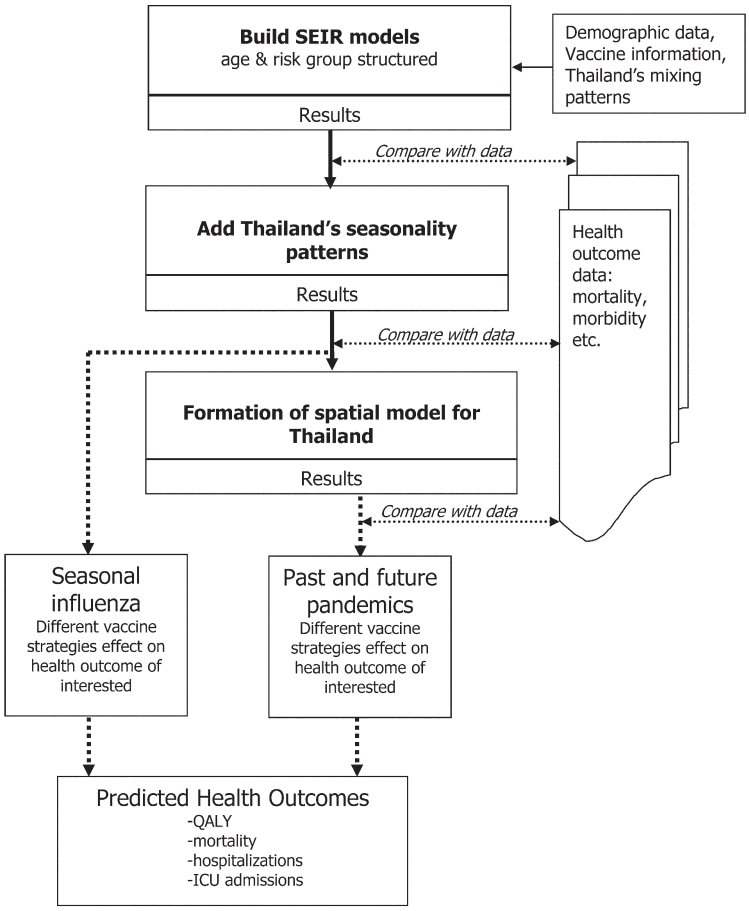


Figure 2 Schematic diagram of the methodology and the information/data that are required for both the model building stage and the estimation impact of various vaccine strategies stage. (Note: predicted health outcomes require assumptions or estimates of age-stratified case fatality rates, case hospitalization rates and case ICU admission rates. Estimating these reliably in a pandemic situation is difficult, but dynamic and statistical modeling techniques can again help[2,18].

For this reason, we propose a framework with three levels of complexity (Figure 2) (each level builds on top of the previous level of complexity): 1) age and risk group-structured transmission dynamic models, 2) models including the seasonal pattern of influenza transmission in Thailand, and 3) model formulations accounting for the spatial structure of influenza transmission in Thailand. The models would be data-driven to ensure that the model predictions are based on real data concerning the influenza-related health outcomes of interest (i.e. age-stratified mortality, hospitalizations, and ICU admissions).

A far more important consideration for most vaccination programmes is appropriately modelling the age structure and the mixing patterns between different age groups[17] and accounting for specific risk groups (those more likely to suffer severe illness if infected). Accurately quantifying seasonal variation and including it in the model would be an essential part of the proposed framework. We also recommend including spatial effects in a relatively simple manner in age and risk group structured models, by dividing Thailand into a small number of interacting sub-populations. The spatial structure would allow us to examine the influence of different demographics and population behaviour in different parts of Thailand.

A validated mathematical model for influenza as proposed (Figure 2) would be useful as a tool for evaluating the direct and indirect effects of vaccination strategies (in terms of health outcomes: age-stratified mortality, quality adjusted life years (QALYs), hospitalizations and ICU admissions) to mitigate and control pandemic and seasonal influenza in Thailand.

Conclusion

A mathematical model for influenza in Thailand could be a very useful tool for evaluating the effects of influenza vaccination strategies to mitigate and control pandemic and seasonal influenza.

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แบบจำลองคณิตศาสตร์ของโรคไข้หวัดใหญ่ A (H1N1-2009) และไข้หวัดฤดูกาลที่เหมาะสมกับประเทศไทยควรมีหรือไม่?

อรุณรักษ์ คูเปอร์ มีใย*

บทคัดย่อ

แบบจำลองทางคณิตศาสตร์จำนวนหนึ่ง สร้างขึ้นโดยคำนึงถึงนโยบายที่เหมาะสมในการจัดสรรวัคซีนป้องกันไข้หวัดใหญ่ในช่วงที่มีการระบาดใหญ่ และประมาณการการจัดสรรวัคซีนที่แตกต่างกันในช่วงฤดูกาลของไข้หวัดประจำปีของประเทศที่สามารถจัดซื้อวัคซีนได้และหรือประเทศในเขตหนาว การประมาณค่าของนโยบายที่เกี่ยวข้องกับการจัดสรรวัคซีนโดยอาศัยแบบจำลองทางคณิตศาสตร์ดังกล่าวช่วยทำให้เราสามารถเลือกนโยบายที่มีประสิทธิภาพมากที่สุดและยังใช้งบประมาณน้อยที่สุดอีกด้วย อย่างไรก็ตามแบบจำลองที่เกี่ยวข้องกับการจัดสรรวัคซีนที่มีอยู่ไม่ได้มีการพิจารณาถึงปริมาณวัคซีนที่มีจำกัดทั้งในระยะสั้นและระยะยาวโดยเฉพาะในประเทศยากจน นอกจากนั้นยังไม่มีแบบจำลองใดที่นำรูปแบบการติดเชื้อไข้หวัดฤดูกาลในประเทศเขตร้อนมาเป็นองค์ประกอบในแบบจำลอง ด้วยเหตุนี้การจัดทำแบบจำลองที่เฉพาะกับประเทศไทยจึงมีความจำเป็นซึ่งจะเป็นประโยชน์ต่อการนำไปใช้และการประเมินนโยบายที่เกี่ยวข้องกับการป้องกันและควบคุมการแพร่ระบาดของไข้หวัดใหญ่และไข้หวัดฤดูกาลโดยใช้วัคซีน นอกจากนี้บทความนี้ยังได้นำเสนอกรอบแนวทางในการพัฒนาแบบจำลองคณิตศาสตร์ของโรคไข้หวัดใหญ่และไข้หวัดฤดูกาลสำหรับประเทศไทยด้วย

คำสำคัญ: แบบจำลองทางคณิตศาสตร์ การระบาดใหญ่ ไข้หวัดใหญ่ ไข้หวัดฤดูกาล วัคซีน

วารสารสาธารณสุขศาสตร์ 2554; 41(1): 77-86

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