COMPUTATIONAL MODELING TO ADDRESS THE BURDEN OF INFLUENZA AND STRATEGIES OF CONTROL MEASURES IN THAILAND

by

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ABSTRACT

Influenza is one of re-emerging infectious disease in Thailand. The true burden of influenza is not known and is needed for influenza preparedness. Thailand has a vaccine policy targeted at healthcare workers (HCWs), people aged 6-24 months or >65 years, people with chronic medical condition (CMC), and pregnant women. However, amount of vaccine is limited and policy planners need information for vaccine prioritization. The government also promotes non-pharmaceutical interventions, but their impact is not well studied. This research aimed to use agent-based model (ABM) to estimate influenza burden in Thailand and assess impact of control measures. The basic reproductive number (R0) based on Thailand's context is unknown and should be estimated for further studies of influenza dynamics. The R0 was estimated using a formula relating the epidemic growth rate (r) and generation time. The projection of influenza burden was studied by fitting an ABM. The model contains a 58,354,744 synthetic Thai population and incorporates people with CMC and HCWs. At start, 100 agents were randomly assigned for initial infection. The model simulated the interactions of individuals with others over 180 days. Impacts of influenza vaccine were simulated at 50%, 75% and 100% coverage. Impacts of face mask wearing and hand washing were simulated at 10%, 25%, 50%, 75% and 100% coverage. The R0 estimates ranged from 1.11 to 1.77 (median 1.39). The highest attack

rate occurs in school-age children and adolescents (15.32%). One Hundred percent coverage of target population policy can avoid morbidity and mortality by 47.06% and 59.61% in total population respectively. However, the benefit is very small for HCWs (3.75% case reduction). The extended policy to include children aged 2-18 years old can avoid >99% of cases. For non-pharmaceutical interventions, at least 50% compliance of the combined face mask use and hand washing policy can avoid morbidity and mortality >98% for all adherence of mask wearing. The public health significance of this research is that it provided information for health policy makers to guide optimized target population for vaccine, and to encourage non-pharmaceutical interventions for controlling influenza outbreak.

Key words: Reproductive number, Influenza, Vaccine, Mask, Hand washing, Thailand, Computer simulation

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1.0 INTRODUCTION

1.1 OVERVIEW

Influenza is a contagious respiratory illness caused by ribonucleic acid (RNA) influenza viruses in members of Orthomyxoviridae. The disease is characterized by fever, headache, myalgia, malaise, sore throat, cough and rhinitis. Influenza in individuals may be indistinguishable from disease caused by other respiratory viruses. The clinical picture may range from the common cold, croup, bronchiolitis, viral pneumonia and undifferentiated acute respiratory diseases.

The virus is transmitted easily from person to person. One method of transmission is via large droplets (>5 μm) that are produced when infected people cough or sneeze.[1] The virus can also be spread by contact transmission. Infected people will often touch their mucus membranes or respiratory secretions before direct interpersonal contact such as hand shaking, or indirect contact such as touching common surfaces. For example, influenza virus was detected on over 50% of the fomites tested in homes and day care centers during influenza season.[2] Uninfected individuals touch these surfaces causing hands contaminated with infected secretions, then touch their mucous membranes and get infection. The incubation period is short, usually 1 - 3 days. Period of communicability is approximately 3-5 days from clinical onset in adults, up to 7 day in young children.

Most people who get the influenza will have mild illness and will recover within one to two weeks without requiring any medical treatment. However, some people are more likely to get influenza complications and require hospitalization. People at high risk for developing complications including children younger than 5 years old (especially children younger than 2 years old), adults 65 years of age and older, pregnant women, and people suffering from medical conditions (such as lung diseases, diabetes, cancer, kidney or heart problems). In these people, the infection may lead to severe complications of underlying diseases, pneumonia and death.

In April 2009, a novel swine-origin influenza A (H1N1) virus was identified and caused outbreaks of influenza in at least 74 countries. It was at this time that the World Health Organization (WHO) declared the start of a new pandemic influenza. These events raised concern and increased interest in better understanding the potential impact of the flu and possible strategies for control measures. Crucial in this planning is an understanding of the basic epidemiology and the transmission dynamics of the disease in various settings, thus leading to potential methods of control for a future pandemic.

Computational models have been used to understand the transmission dynamics of influenza.[3-5] They have also been used as health policy tools to predict the effect of public health interventions on mitigating future epidemics or pandemics.[6-8] The models can project plausible scenarios, compare and guide control strategies. Many studies generated models in developed countries or in developing countries using basic reproductive number (R_0) which was estimated from influenza outbreak in these countries. However, there are limited information of influenza transmissibility in social contact pattern of Southeast Asia countries including Thailand. Thailand needs reliable information of influenza burden that specific to Thailand disease dynamics for influenza preparedness. The understanding of transmission dynamics and

determinants of seasonality should assist in developing better-focused prevention and control strategies for annual endemic outbreaks and influenza pandemics.

This study will determine influenza burden in no-intervention scenario, intervention to prevent outbreak, and intervention to control outbreak.

1.2 EPIDEMIOLOGY OF INFLUENZA

Three types of influenza virus are recognized: A, B and C. Influenza A is associated with widespread epidemics and pandemics; Influenza B is infrequently associated with regional or widespread epidemics; Influenza C is associated with sporadic cases and minor localized outbreaks. Influenza A viruses can be subtyped according to the antigenic and genetic nature of their surface glycoproteins; 16 hemagglutinin (HA) and 9 neuraminidase (NA) subtypes have been identified to date.[9] Viruses bearing all known HA and NA subtypes have been isolated from avian hosts, but only viruses of the H1N1, H2N2, and H3N2 subtypes have been associated with widespread epidemics in humans. Different subtypes have not been identified among influenza B and C viruses.

The long-term maintenance of influenza viruses in the human population is due to antigenic variation that takes place in the HA and NA surface glycoproteins of the virus. Antigenic variation causes an individual susceptible to new strains despite previous infection by influenza viruses or previous influenza vaccination. There are two type of the variation, antigenic drift and antigenic shift. A first type of variation, antigenic drift, is a process by which the accumulation of point mutations in the HA and NA genes in influenza A. During antigenic drift, a variety of mutations including substitutions, deletions, and insertions produce genetic variation

in influenza viruses. These mutations occur because a viral RNA polymerase that lacks proofreading activity transcribes the influenza genome. Thus, non-deleterious errors that occur during genome replication may be preserved and subsequently amplified if conditions favor their survival. These genetic changes often encode amino acid changes in the surface proteins that permit the virus to escape neutralization by antibody generated to previous strains. This type of variation is responsible for frequent epidemics and regional outbreaks and necessitate annual reformulation of influenza vaccine.

A second type of variation, antigenic shift, occurs at irregular intervals and only among influenza A viruses and describes a major antigenic change whereby a virus with a new HA (with or without a new NA) is introduced into the human population. Antigenic shift occurs in at least two ways. It may occur when an animal or avian influenza A virus is transmitted without reassortment from an animal reservoir to humans or when a progeny virus with a new HA (with or without a new NA) arises as a result of genetic reassortment between animal and human influenza A viruses. This type of variation is responsible for pandemics influenza.

Influenza occurs in both pandemic and interpandemic forms. Pandemics, defined as sustained spread of new influenza shift variants in at least 2 WHO regions. There were three pandemics in the 20th century. Morbidity and mortality due to influenza are usually particularly high during the occasional global pandemic. The mortality burden of the 1918 A(H1N1) pandemic or 'Spanish flu' was estimated at least 20 million deaths, globally;[10] followed by the 1957 H2N2 'Asian flu' and 1968 H3N2 'Hong Kong flu' pandemics which had less severity. On the other hand, in the years between influenza pandemics, which are called interpandemic periods, influenza epidemics occur almost every year, following a regular seasonal pattern in temperate zones and are called seasonal influenza. The seasonal influenza is usually less severe

in its impact compared to pandemic influenza, but can also show considerable between-year variation.

1.2.1 Influenza seasonality

Each year, influenza A and/or B viruses circulate during winter months in the temperate climates of the Northern and Southern hemispheres, overtly causing extensive epidemics of acute respiratory infections (ARI) in 5%-15% of the total population. The WHO estimates the average global burden of seasonal influenza comes to be on the order of 600 million cases, 3 million cases of severe illness and 250,000 - 500,000 deaths per year.[11] Most seasons dominated by influenza A(H3N2), while influenza A(H1N1) and influenza B seasons are usually less prevalent and less severe.[12] Localized epidemics within a community often have a characteristic pattern in which the epidemic begins abruptly, peaks within 2 to 3 weeks, and has a total duration of 5 to 10 weeks.[13]

The influenza seasonal pattern varies depending on the region in the world. In temperate climate zones, influenza epidemic is generally seasonal: the disease is thought to exist at a low level throughout the year, with activity increasing in the late fall and peaking in mid-winter. In the Northern Hemisphere, influenza outbreaks and epidemics typically occur between November and March, whereas in the Southern Hemisphere, influenza activity occurs between April and September.[14] For the tropical zones, seasonal patterns are less pronounced and influenza virus can be more easily identified throughout the year, with a possible peak in June to August during the hot rainy season.[15,16]

To date, mechanisms contribute to influenza seasonality remain unclear. Some mechanisms have been proposed to explain the seasonality including contact rates, virus survival, and host immunity.

- Contact rates

Increased proximity between susceptible and infected individuals is frequently suggested to be an important factor of influenza virus transmission. The person-to-person spread of aerosol particles is greatly enhanced by crowding of susceptible individuals around each infective subject, thereby maximizing the potential for the spread of infection.

Increasing risk of disease transmission has been observed among group of travelers. Baker et al. investigated pandemic influenza A/H1N1 2009 influenza outbreak on passenger aircraft and considered 107 passengers seated in the rear section of the plane to be susceptible cohort. They estimated the overall risk of in-flight infection in the rear section of the plane to be 1.9% (95% confidence interval 0.3% to 6.0%). For the 57 passengers sitting within two rows of the laboratory confirmed symptomatic cases the risk was higher at 3.5% (0.6% to 11.1%).[17] Han et al. investigated an outbreak of influenza A pandemic (H1N1) 2009 occurred among 31 members of a tour group in China. They found that for the 16 tourists who had talked with the index influenza case-patient from close range (<2 m) for >2 minutes, the attack rate was 56%, whereas none of the 14 tourists who did not talk with the index case became ill. Members of the tour group who had talked with the index influenza case-patient for >10 minutes were almost 5 times as likely to become ill than those who had talked with her for 2–9 minutes.[18]

People may spend more time indoor together when weather is not good, such as cold or rainy days, this will increase contact rate among individuals. Graham et al. conducted a study using the US Environmental Protection Agency's Consolidated Human Activity Database

(CHAD) for various locations in the United States and demonstrated that individuals spend on average 51 - 86 more minutes indoors during cold weather and spend on average 36 minutes more time indoors during rainy weather.[19]

- Virus survival

Influenza virus can be transmitted through several modes including droplet, aerosols, and contact transmission (both direct and indirect contact). The virus must be able to survive in a variety of environmental conditions for effective transmission among hosts. Several conditions were considered as important factors related to virus survival and seasonality. The high level of humidity, high temperature, and solar radiation demonstrated decreasing of influenza virus survival.[20-22]

Lowen et al. experimented the effect of temperature and relative humidity on aerosol transmission among guinea pigs. They found that aerosol spread of influenza virus was dependent upon both ambient relative humidity and temperature. The low relative humidities of 20% - 35% were most favorable for transmission, while transmission was completely blocked at a high relative humidity of 80%. Furthermore, when guinea pigs were kept at 5°C, transmission occurred with greater frequency than at 20°C, while at 30°C, no transmission was detected.[20] These finding implicate low relative humidities produced by indoor heating and cold temperatures as features of winter that favor influenza virus spread. However, it is unlikely this finding can explain influenza seasonality in the tropics because those regions are typically humid year-round, and epidemics tend to occur during the rainy season, when humidity is typically at maximal levels. Lowen et al. also reported that the lack of aerosol transmission among guinea pigs at 30°C at all humidities and transmission via the contact route was equally efficient at 30°C and 20°C. This implies that contact or short-range spread predominates in the tropics and offers

an explanation for the lack of a well-defined, recurrent influenza season affecting tropical and subtropical regions.[21]

Sagripanti et al. calculated the expected inactivation of influenza A virus by solar ultraviolet radiation in several cities of the world during different times of the year. The inactivation rates indicated that influenza A virions should remain infectious after release from the host for several days during the winter "flu season" in many temperate-zone cities, with continued risk for human infection.[22] This might explain increasing of influenza burden during seasons with reduced sun activity, such as winter season in temperate regions and rainy season in tropics.

- Host immunity

Evidence for seasonal triggers of host immunity suggesting that respiratory infections including influenza are more frequent in individuals with known vitamin D deficiencies.[23] Human vitamin D levels are generally dependent upon exposure to solar radiation. Vitamin D deficiencies are common in temperate populations during the winter when solar radiation is lowest. Large seasonal variations in vitamin D levels have been found in some studies. Guillemant et al. found a difference between after summer and after winter 25-hydroxyvitamin D (25(OH)D) levels to be around 30 nmol/l in French male adolescents.[24] Vieth et al. found an average difference between summer and winter 25(OH)D levels at 18 nmol/l in a study among Canadian women; and prevalence of vitamin D insufficiency was higher in winter time, especially among Asian ethnics.[25]

One observational study has shown that individuals with lower vitamin D levels are significantly more likely to report respiratory infections. Ginde et al. performed a secondary analysis of the Third National Health and Nutrition Examination Survey (NHANES), a

probability survey of the US population conducted between 1988 and 1994. They examined the association between 25(OH)D levels and recent upper respiratory tract infections (URIs) in 18,883 participants 12 years and older. They found that lower 25(OH)D levels were independently associated with recent URTI (compared with 25[OH]D levels of ≥30 ng/mL: odds ratio [OR], 1.36; 95% CI 1.01 to 1.84 for <10 ng/mL and 1.24; 1.07 to 1.43 for 10 to <30 ng/mL).[26] This association was supported by a recent clinical trial. Urashima et al. conducted a randomized control trial to test the effect of vitamin D supplementation on influenza A and B incidence in school children in Japan. The study indicated that the experimental group were significantly less likely to become infected with influenza A than the controls. Influenza A occurred in 18 of 167 (10.8%) children in the vitamin D group compared with 31 of 167 (18.6%) children in the placebo group [relative risk (RR), 0.58; 95% CI: 0.34 to 0.99; p = 0.04]. However, the incidences of influenza B and rapid influenza diagnostic test-negative influenza-like illness were not significantly different between the vitamin D and placebo groups.[27] Another randomized controlled trial found no benefit of vitamin D supplementation in decreasing the incidence or severity of symptomatic URTIs during winter. Li-Ng et al. conducted a control trial to determine whether vitamin D supplementation during the winter season prevents or decreases URI symptoms in 162 adults who were randomly assigned to receive 50 μg vitamin D3 (2000 IU) daily or matching placebo for 12 weeks. A bi-weekly questionnaire was used to record the incidence and severity of URI symptoms. There was no difference in the incidence of URIs between the vitamin D and placebo groups (48 URIs *vs*. 50 URIs, respectively, p = 0.57). There was no difference in the duration or severity of URI symptoms between the vitamin D and placebo groups [5.4 ± 4.8 days *vs.* 5.3 ± 3.1 days, respectively, p = 0.86 (95% CI for the difference in duration −1.8 to 2.1)].[28]

1.2.2 Populations at risk for influenza transmission and disease burden

- People who are at high risk of getting influenza illness

The disease can affect all age groups; however, influenza infection is higher among young children and elderly.

  - Children

Attack rate and hospitalization of influenza are higher among pre-school and school-age children. Data collected using medical records identification confirm that younger children are at elevated risk of influenza hospitalization; especially to those under 2 years of age, and the highest risk is in children under age 6 months.[29-32]

  - People who live with or care for others who are high risk of contracting influenza, such as healthcare workers

Healthcare workers are at risk of acquiring influenza and spread the contagious influenza virus to patients under their care and can be key cause of outbreak in healthcare settings. This is particular troubling for many patients at high risk for influenza-related complications such as those who have chronic medical conditions. Cross-transmission of influenza infection from healthcare workers to patients has been described.[33-36]

- People who are at high risk of developing serious complications if they get sick with influenza

  - Elderly

Influenza morbidity is also higher among elderly. Thompson et al. studied influenza-associated hospitalizations in the United States and reported that persons 85 years or older had the highest rates of influenza-associated primary respiratory and circulatory hospitalizations

(1,194.9 per 100,000 persons), followed by children younger than 5 years (107.9 primary respiratory and circulatory hospitalizations per 100,000 persons).[37]

Similar incident pattern was observed in developing countries. Simmerman et al. analyzed data from identified all hospitalized pneumonia patients form a population-based surveillance system in 2 provinces of Thailand and reported the average annual incidence of influenza pneumonia was greatest in persons age 75 or older (375 per 100,000) and in children less than 5 years of age (236 per 100,000).[38] The elderly suffer by far the highest serious illness from influenza. The influenza-associated mortality was highest in persons aged 65 years and older, who account for about 90% of deaths attributable to influenza.[39,40]

- People who have certain medical conditions

Influenza also can make chronic diseases worse. These medical conditions include chronic lung diseases (such as chronic obstructive pulmonary disease (COPD)), and heart disease (such as congenital heart disease, congestive heart failure and coronary artery disease), asthma, and endocrine disorders (such as diabetes mellitus (DM)).

When overall influenza attributable mortality is examined by comparing deaths above seasonal baseline in years of high influenza versus low influenza activity, ischemic heart disease account for 22.9% of the attributable excess mortality, COPD and other heart disease has been the cause of death in 13.8% and 9.1% respectively.[41] A similar finding was reported in by Yap et al. who conducted a retrospective study to estimate excess hospital admissions for pneumonia, COPD, and heart failure during influenza seasons in Hong Kong. The adjusted rates of excess influenza-associated hospital admissions for the three diagnoses combined amounted to 58.5, 20.0, 29.2, and 13.4 per 10,000 populations aged $\geq$ 65 years in 1998, 1999, 2000, and 2001, respectively.[42]

Several studies have revealed an association between heart diseases and severe illness of influenza. de Roux et al. conducted a study among patients with viral community-acquired pneumonia (CAP) and found that patients with chronic heart failure have an increased risk of acquiring a viral CAP (OR 15.3; 95% CI 1.4 to 163; $p = 0.024$).[43] This finding was similar with that of a study that found influenza caused a seasonal excess mortality in patients with underlying cardiac illness. In this study, influenza-attributable risk of acute cardiopulmonary hospitalizations and death was estimated at 10.3 (95%CI 5.9 to 14.7) comparing influenza season to peri-influenza season.[44]

- Pregnant women

Pregnant women have an increased risk of influenza infection and complications and lead to increase medical visits and hospitalizations for influenza-related illness relative to women of the same age.[44,45]

A large study of women aged 15–44 years who were enrolled in the Tennessee Medicaid program during influenza seasons between 1974 and 1993 demonstrated that pregnancy increased the risk of hospitalization for pneumonia, influenza and cardiopulmonary conditions; the risk increased during the later stages of pregnancy.[45] This study reported influenza-attributable risks for hospitalization in comparable non-pregnant and postpartum women were 1.91 (95%Cl 1.51 to 2.31) and 1.16 (95%Cl -0.09 to 2.42) per 10,000 women-months, respectively. A recent 13-year (1990–2002) population-based cohort study reported similar findings. The rate of hospital admissions because of respiratory illness in the third trimester among women without co-morbidities was 7.4 per 10,000 woman-months during the influenza season, compared with 5.4 and 3.1 per 10,000 woman-months during the peri-and non-influenza seasons respectively.[46]

1.3 INFLUENZA IN THAILAND

1.3.1 Influenza surveillance in Thailand

There are two major surveillance systems for influenza in Thailand. The first is an influenza cases surveillance conducted by the Bureau of Epidemiology (BoE), Thai Ministry of Public Health (MoPH). The second is an influenza virological surveillance conducted by the Thailand National Institute of Health (NIH), Thai MoPH.

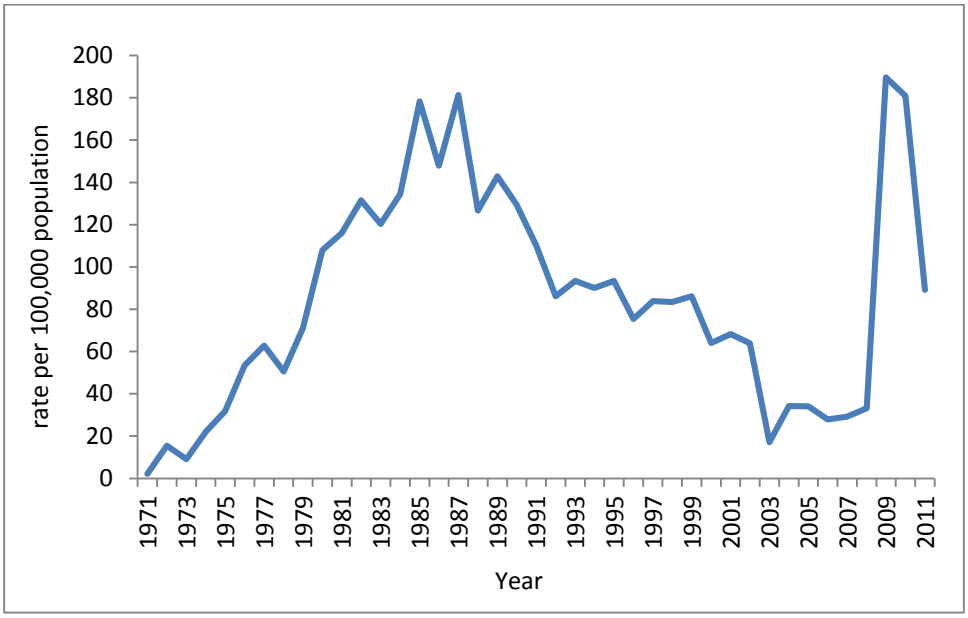
Influenza is one disease in the National Notifiable Disease Report named Report506. The surveillance of influenza is hospital-based passive surveillance, mostly is governmental hospitals. When a patient visits a healthcare facility for medical treatment and is diagnosed with influenza, disease surveillance officials collect information (demographic data, diagnosis, date of onset, hospitalization, etc) and enter the data into Notifiable Disease Report database. The electronic database is sent from each hospital in that province to the Provincial Health Office. Then, the data are merged and sent to the BoE. The responsible officials must report even suspected disease or syndrome without laboratory confirmation (the system allows for a later revised report after laboratory result become available). A strength of this system is that it is quick to detect abnormal events including emerging diseases and outbreaks. However, because testing for influenza infection is not routinely available, very few reported cases are ever confirmed in the laboratory. As a result, influenza reported cases tend to be influenza-like illness (ILI). Because the majority of ILI cases are not caused by influenza, the lack of laboratory confirmation for influenza cases could result in over-estimates of influenza infections.

Influenza virological surveillance is a sentinel laboratory-surveillance in Thailand. The NIH participates in the WHO influenza laboratory network as a national influenza center by

conducting laboratory surveillance, subtyping viruses responsible for disease outbreaks, and contributing strain surveillance data. Clinical samples are submitted by ten participating hospitals from all 4 regions (North, Northeastern, Central and South) and 1 health center in Bangkok. These sentinel hospitals also must send influenza cases report to the National Notifiable Disease Report system. However, the responsible officials are laboratory officials and this is an independent surveillance system. If someone is laboratory positive on the virological surveillance system, and is notified to surveillance officials, the case will get into the Notifiable Disease Report database.

1.3.2 Incidence of influenza in Thailand

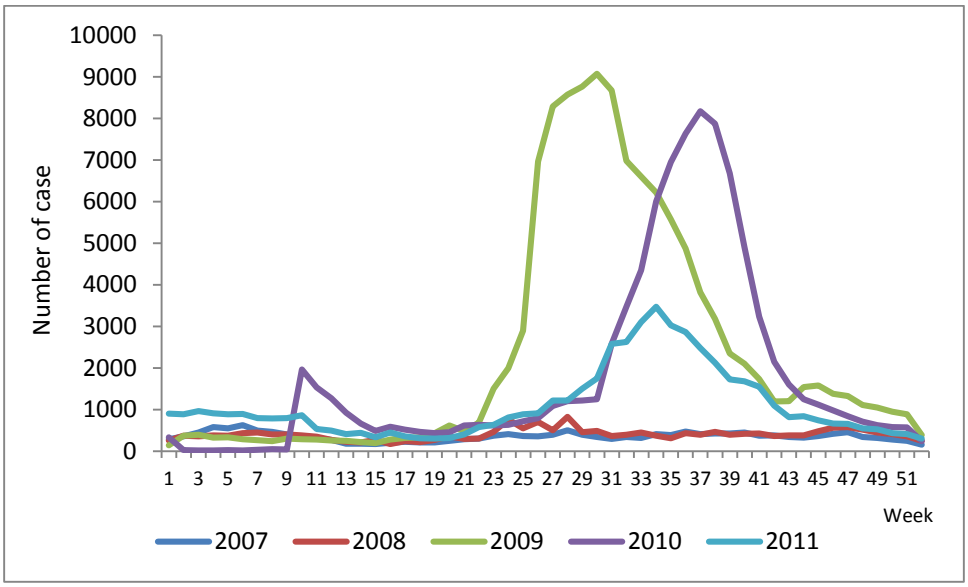
Thailand had reported influenza cases with incidence of 2.17 per 100,000 population in year 1971. The incidence increased gradually and peaked between 1982-1989 (120.41-178.36 per 100,000 population). Then, the reported cases have generally declined except for the epidemic between year 2009-2010, a result of pandemic novel influenza A (H1N1). During the pandemic the incidence was 189.72 and 180.82 per 100,000 population in year 2009 and 2010 respectively (Figure 1).



Source: Bureau of Epidemiology, Thailand MoPH

Figure 1 Reported incidence of influenza per 100,000 population, Thailand 1971-2011

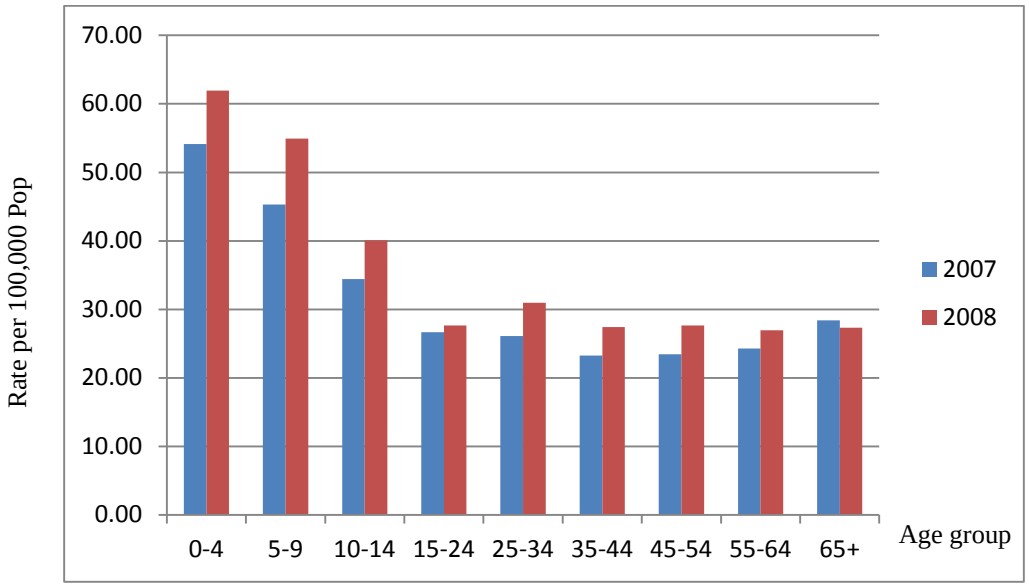
Typically there is a peak of reported cases during the rainy season, between July-September (around Week 30th - 40th), except in 2009 when the epidemic came early (Figure2).



Source: Bureau of Epidemiology, Thailand MoPH

Figure 2 Reported cases of influenza, by week of onset, Thailand 2007-2011

Before the pandemic years, influenza incidence was high among small children. In 2007, the highest incidence was found in age group 0-4 years old (54.16 per 100,000 population); followed by age group 5-9 years old (45.32 per 100,000 population), and age group 10-14 years old (34.43 per 100,000 population) respectively. In 2008, the highest incidence was found in age group 0-4 years old (61.92 per 100,000 population); followed by age group 5-9 years old (54.95 per 100,000 population), and age group 10-14 years old (40.06 per 100,000 population) respectively (Figure 3).

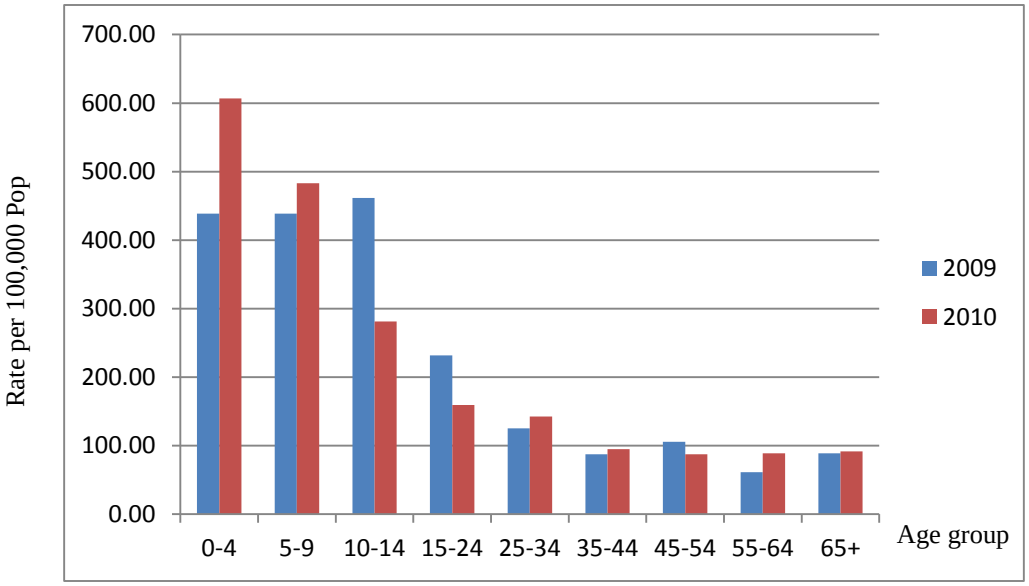


Source: Bureau of Epidemiology, Thailand MoPH

Figure 3 Reported incidence of influenza per 100,000 population, by age group, Thailand 2007-2008

During the pandemic years, influenza incidence shifted to older children in 2009 and shifted back to small children in 2010. In 2009, the highest incidence was found in age group 10-14 years old (461.31 per 100,000 population); followed by age group 5-9 years old (438.59

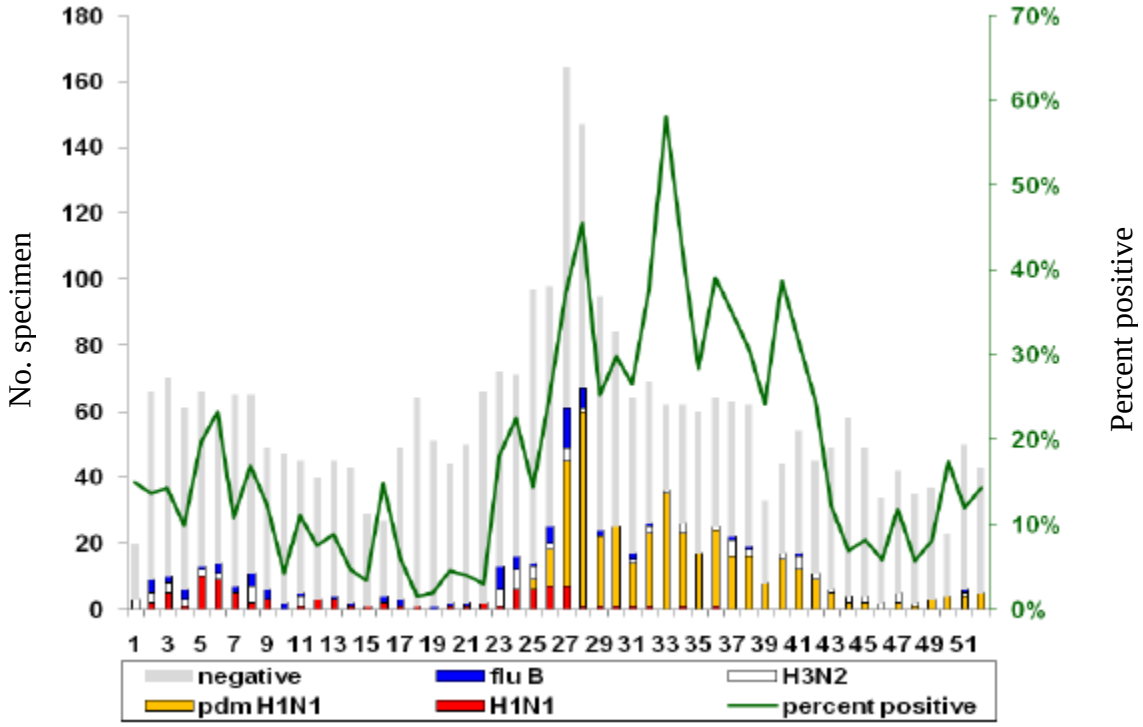
per 100,000 population), and age group 0-4 years old (438.46 per 100,000 population) respectively In 2010, the highest incidence was found in age group 0-4 years old (606.75 per 100,000 population); followed by age group 5-9 years old (483.2 per 100,000 population), and age group 10-14 years old (281.33 per 100,000 population) respectively (Figure 4).



Source: Bureau of Epidemiology, Thailand MoPH

Figure 4 Reported incidence of influenza per 100,000 population, by age group, Thailand 2009-2010

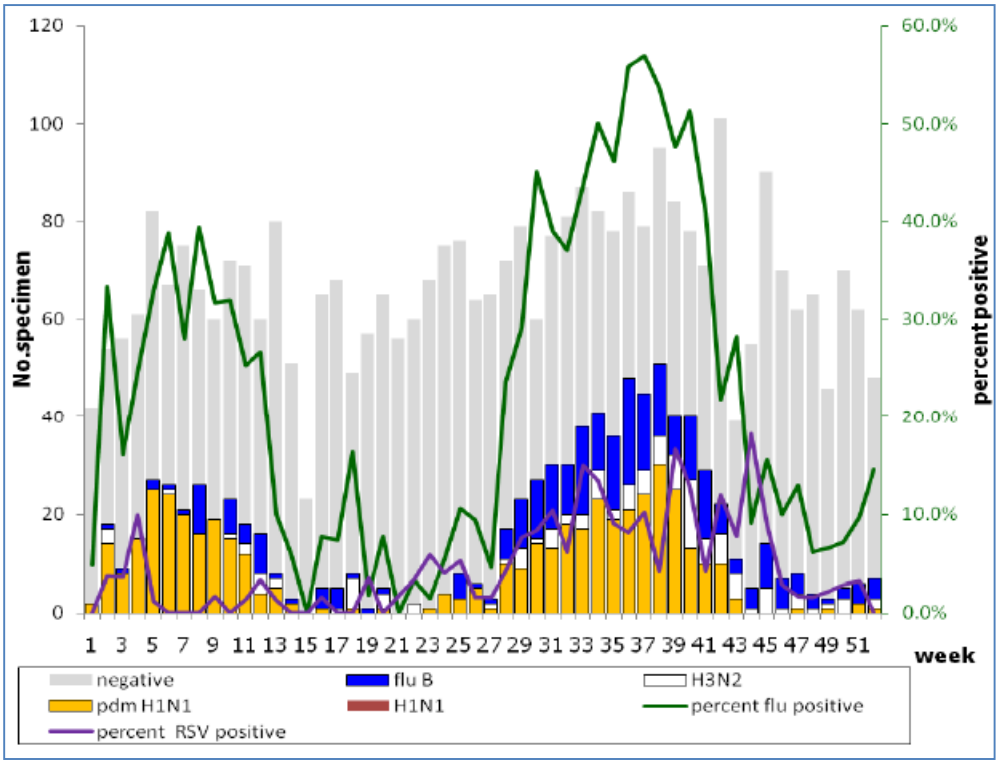
In 2009, Thai NIH received 3,052 clinical specimens from ILI patients, 638 (20.9%) had positive results. Of these, there was seasonal H1N1 88 specimens (13.79%), H3N2 80 specimens (12.54%), Flu B 78 specimens (12.23%), and pandemic H1N1 392 specimens (61.44%) (Figure5).



Source: Thai National Influenza Center, Thailand NIH

Figure 5 Number of clinical specimens from ILI patients and test results, influenza virological surveillance, Thailand 2009

In 2010, Thai NIH received 3,505 clinical specimens from ILI patients, 866 (24.7%) had positive results. Of these, there was H3N2 119 specimens (13.74%), Flu B 285 specimens (32.91%), pandemic H1N1 462 specimens (53.35%), seasonal H1N1 was not identified (Figure6).



Source: Thai National Influenza Center, Thailand NIH

Figure 6 Number of clinical specimens from ILI patients and test results, influenza virological surveillance, Thailand 2010

1.4 INFECTIOUS DISEASE MODELING

Mathematical models are being increasingly used to explain the transmission of infections and to evaluate the potential impact of control strategies in reducing morbidity and mortality. They can integrate epidemiological and biological data to give quantitative insights into patterns of disease spread and the effectiveness of interventions. Their application include predicting the impact of interventions against common diseases as well as determining optimal control strategies against emerging infectious diseases. Many models were used to make predictions about the likely outcome of alternative courses of public health interventions for global concerned diseases such as Severe Acute Respiratory Syndrome (SARS), Human Immunodeficiency Virus (HIV), small pox, and influenza.[47-49]

The model structure reflects the natural history of the infections. In this structure, population categories and diseases transitions need to be described. Individuals are classified according to theirs infection and immune status as either susceptible, exposed, infectious, or recovered.

- Susceptible (S): Initially, individual is susceptible and can get infection if they are exposed to pathogen of infectious individuals.
- Exposed (E): In early stages of infection, the infected individuals may not exhibit obvious signs of infection and pathogen may be too low to allow further transmission. Infected individuals are not yet infectious.
- Infectious (I): At this stage, the infected individuals become infectious and can spread the disease to any susceptible individual that they come contact with.
- Recovered (R): The individuals have recovered from the disease and no longer infectious

1.4.1 Epidemic dynamics

The growth of an epidemic is principally governed by two factors: the basic reproduction number (R_0) and generation time. R_0 determines how intensive strategies will need to be to control the epidemic, whereas both R_0 and generation time determine the time available to implement suitable control measures.

1.4.1.1 Basic reproductive number (R_0)

This number quantifies the transmissibility of any pathogen, which is defined as the average number of secondary infectious persons resulting from one infectious person following their introduction into an entirely susceptible population. A disease can spread if R_0 is greater than one, and the transmission will be inevitably die out if R_0 is less than one. The goal of control policies is to reduce R_0 to below one by eliminating a proportion 1 - 1/ R_0 of transmission. This can be achieved in three ways:[7]

- by reducing contact rates in the population such as social distance measures
- by reducing the infectiousness of infected individuals such as treatment of isolation
- by reducing the susceptibility of uninfected individuals such as vaccination or antiviral prophylaxis

The value of R_0 is different for different infectious agents and depends among other things on the characteristics of the population that the agent invades. Given this, it is not immediate that one can adopt previously determined values or size ranges for an outbreak in a new population unless many of the complicated characteristics of, for example, population composition and contact structure are comparable.[50]

Many modeling studies have estimated R_0 either previous influenza pandemics or seasonal influenza. The estimated influenza R_0 range from 1.2 to 3.75 (Table 1).[51-59]

Table 1 Summary of influenza R_0 estimation

Authors	Type	Country	Study year	R_0
Chowell (2006)	Pandemic 1918	Switzerland	1918 (spring) 1918 (fall)	1.49 (95% CI 1.45 - 1.53) 3.75 (95% CI 3.57 - 3.93)
Mills (2004)	Pandemic 1918	USA	1918	Median 2.0 (IQR 1.7 - 2.3)
White (2008)	Pandemic 1918	USA	1918	Range 1.34 - 3.21
Massad (2007)	Pandemic 1918	Brazil	1918	2.68
Vynnycky(2008)	Pandemic 1957	UK	1957	1.8
Viboud (2006)	Epidemic	UK	1951	Range 1.9 - 2.5
Lessler (2007)	Outbreak	USA	1976	1.2 (Range 1.1 - 1.4)
Chowell (2008)	Seasonal	USA, Australia, France	1972 - 1997	1.3 (95% CI 1.2 - 1.4) Range 0.9 - 2.0
Fraser (2009)	Novel influenza A (H1N1)	Mexico	2009	1.4 - 1.6

1.4.1.2 Generation time

Generation time (T_g) is the time form onset of such a primary to a secondary case. It is determined by the duration of the pre-infectious and infectious periods (which determine when infection leaves the primary case) as well as the incubation period (which determines when the secondary case has clinical onset). The generation time also referred to as the serial interval. Estimates of the serial interval of human influenza are incorporated into models of influenza as

the generation time, which is formally defined as the average time interval between successive infections in a chain of transmission. Estimates of the mean serial interval range between 2 - 4 days.[57,60]

1.4.2 Models

A models provides a convenient framework in which we can put all key factors together to make predictions of changes in the number of susceptible, infectious, and immune individuals and the likely number of cases by time of interests. There are two types of models to be considered, deterministic and stochastic.

1.4.2.1 Deterministic model

Deterministic models describe what happens, on average, in a population of interest. In these models, the input parameters (such as contact rate, rate of infection, duration of disease, or rate of recover, etc.) are fixed, and therefore the model's predictions (such as number of cases, number of recovery or immune) represent an average number over time.

A commonly used deterministic model for epidemiological study, is the susceptible-infectious-recovered (SIR) and susceptible-exposed-infectious-recovered (SEIR) compartmental model. This type of model categorize the host population to infection status as either susceptible, exposed, infectious, or recovered. Fundamental to the deterministic model are assumptions that all susceptible people in the population are equally at risk of infection from any infected individual (homogeneous mixing) and that all infected individuals have a constant and equal infectiousness.

Although compartmental SIR models have proven to be quite useful in modeling epidemics, they do not properly model some important aspects of disease spread. For example, assuming homogeneous mixing of the population is unrealistic. Individuals tend to make contact with household members, workplace colleagues and friends at a much higher rate than random strangers, and such regular contacts will also tend to be in the same geographic vicinity. Also, contact with infectious individuals is much higher at hospitals. One example of this limitation of assuming homogeneity; consider the 2002-2003 outbreak of SARS. Using a deterministic model to estimated R_0 based on the initial outbreak of SARS would estimate a very high number of SARS patients, with cases numbering easily in the millions. However, the actual reported of SARS cases was much lower. This resulted from the estimation of R_0 were based on data involving large numbers of transmission in hospitals, where people have usually high rate of contact.[61]

1.4.2.2 Stochastic model

Stochastic models allow the number of individuals who move between compartments to vary by chance. The input parameter may vary randomly. This is crucial when heterogeneity of key factors among population is expected. Also, most interventions are usually considered to be heterogeneous among population. Therefore, the stochastic models are more realistic than deterministic models. The model's prediction will give a range of output number over time. This feature of stochastic models is practical for decision-making purposes, for example, the range of number of cases (both no-intervention and intervention scenarios) is more helpful for planning purposes than the fixed average number of cases.

The agent-based model is one type of stochastic model. Agent-based models keep track of what happens to every individual in a population and allowing chance to determine whether or

not an individual is infected. This approach is to draw a number at random for each individual, and to specify the range in which it the random value should lie for the individual to be considered as infected. If the number falls outside the range, then that individual remains susceptible. This range is based on the risk of infection at that time point. To calculate the outbreak size in a given population, the method would need to draw random numbers for each susceptible person, update the number of susceptible and infectious individuals based on the random number drawn, and repeat this process until there are no further infectious or susceptible individuals and transmission ceases.

For many infectious diseases, transmission occurs mainly between people who are collocated (simultaneously in the same location), and spread is due mainly to people's movement. In addition, diseases often spread differently in different age groups, spread differently depending on the type of contact; for example, contacts at home tend to be more intimate than contacts at work. Also, disease spread is affected by geographic location and seasonality. Researchers have built very high-fidelity models using agent-based simulations, where each of these important characteristics is included in the model.[7,62]

1.4.3 Influenza modeling

The use of modeling and simulation for influenza is well recognized. Many models have been used to understand the transmission dynamics of influenza, find the optimal policies to minimize the mortality and morbidity of epidemic outbreaks, and as a health policy tool to predict the effect of public health interventions.

- Estimation of epidemiological parameters

Many modeling studies have investigated the past influenza epidemics and historical pandemics of the 20th century: the Spanish Flu 1918–1919 (H1N1) and Asian Flu 1957–1958 (H2N2) and have consistently estimated that R_0 was mostly in the range of 1.2–3 (Table 1).[51-58]

- Assessing the effectiveness of biomedical and behavioral public health interventions

The potential effectiveness of antiviral agents have been modeled to assess their effectiveness and compare the relative effectiveness of prophylaxis versus treatment strategies (Table 2),[7,8,63-66] and to assess the potential risk of antiviral resistance (Table 3).[67-70] These studies consistently showed that targeting antiviral prophylaxis (that is, providing close contacts of suspected cases with antivirals) would be an efficient use of antiviral stockpiles in terms of reducing the epidemic size, compared with treatment-only strategies. These finding are crucial in decision making on the best use of country's antiviral stockpiles.

Table 2 Studies model an effectiveness of antiviral agents

Authors	Type	Findings
Longini (2004)	Treatment & prophylaxis	Treating index case and prophylaxis of contacts reduce attack rate in the population from 33% to 2%
Ferguson (2005)	Prophylaxis	• prophylaxis of an entire country or region should be able to eliminate a pandemic virus with an $R_0 \geq$ of 3.6 • Social targeting prophylaxis that initiated after 20 or more cases, has a 90% probability of eliminating the pandemic strain if $R_0 \leq 1.25$
Longini (2005)	Treatment & prophylaxis	Treating index case and prophylaxis of contacts would have a high probability of containing influenza if $R_0 < 1.25$
Ferguson (2006)	Prophylaxis	Antiviral prophylaxis of household members is effective in reducing cumulative attack rates by at least one-third and peak attack rates by a half
van den Dool (2009)	Prophylaxis	Post-exposure and continuous prophylaxis reduced the patient infection attack rate from 0.19 to 0.13 and 0.05, respectively.
McCaw (2007)	Treatment & prophylaxis	• Targeted post-exposure prophylaxis delays the onset of the pandemic • Treatment based strategy does not delay the onset of a pandemic, and is not capable of significantly reducing the attack rate from baseline

Table 3 Studies model a potential risk of antiviral resistance

Authors	Pattern of usage of antivirals	Findings
Furguson (2003)	Treatment of 6% of symptomatic influenza infections	Resistance will occur in 1.8% of the treated patients, or 0.049% of all symptomatic influenza infections for the first 3 years after treatment is introduced in the population.
Lipsitch (2007)	Treatment of 30% of infected hosts, and/or prophylaxis of 30% of contacts	Even if antiviral treatment or prophylaxis leads to the emergence of a transmissible resistant strain in as few as 1 in 50,000 treated persons and 1 in 500,000 prophylaxed persons, widespread use of antivirals may promote the spread of resistant strains to a prevalence of tens of percent by the end of a pandemic
McCaw (2008)	Combined treatment (40%) and prophylaxis (30%)	Strategies that combine treatment and prophylaxis are most effective at controlling transmission, at the cost of facilitating the spread of resistant viruses
Arino (2009)	40% or 60% treatment level	These treatment levels can result in a more rapid depletion of drug stockpiles, leading to run-out, by promoting wide-spread drug resistance

Vaccination is the long-term solution for reducing morbidity and mortality of influenza. A series of studied used mathematical modeling to assess the public health benefit of different vaccination strategies to optimize the use of a limited amount of vaccines (Table 4).[71-74] Most

studies concluded that vaccinating school children would substantially reduce influenza transmission.

Table 4 Studies model optimal vaccine distribution

Authors	Target population	Findings
Patel (2005)	Age group: 0-4, 5-18, 19-50, 51-64, 65+ years	When there was only enough vaccine for 30% of the entire vaccination and the objective was to minimize illness, the optimal vaccination strategy involved concentrating vaccine in children, with the leftover vaccine going to middle aged adults
Riley (2007)	General population	A lower (optimal) vaccine dose may be justified in order to increase population coverage, thereby reducing the infection attack rate overall
Basta (2009)	Children aged 6 months to 18 years	Vaccinating school-aged children against influenza can reduce age-specific and population-level illness attack rates
Lee (2010)	Age group: 0-5 months, 6-23 months, 2-4.9 years, 5-18 years, 19-24 years, 25-49 years, 50-64 year, 65+ years	Optimal allocation is adherence to the Advisory Committee on Immunization Practices (ACIP) prioritization recommendations for the H1N1 influenza vaccine when vaccine is in limited supply and that within the ACIP groups, children should receive highest priority

The effect of public health interventions such as closing schools, quarantining infected individuals or imposing travel restrictions also have been modeled (Table 5).[7,8,64,75] The studies showed that that household quarantine, and prolonged school closures, could reduce the cumulative number of influenza cases.

Table 5 Studies model an effectiveness of public health interventions

Authors	Interventions	Findings
Ferguson (2005)	School and workplace closure (add on antiviral prophylaxis policy)	Adding area-based school and workplace closure to a antiviral drug-sparing prophylaxis policy increases policy effectiveness significantly, with the combined policy having a 90% chance of elimination for $R_0 = 1.7$
Longini (2005)	Quarantine (add on antiviral prophylaxis policy)	Combination of 80% targeted antiviral prophylaxis and quarantine is effective at an *R*0 as high as 2.4
Ferguson (2006)	Case isolation	Isolating 90% of influenza cases can reduce cumulative attack rates from 34% to 27% for $R_0 = 2.0$
Epstein (2007)	International air travel restrictions	95% travel restrictions can delay the initial spread of the epidemic, as measured by the number of cases after 6 months

Most of influenza modeling studies utilized compartmental models; however, some of the more recent studies conducted utilize agent-based simulation models.[6-8,64,74,76,77] Agent-based simulations can easily take into account household demographics, individually targeted

interventions and spatial heterogeneity which are often difficult simulate using compartmental models. However, it needs intensive computer resources and take times to run the models, especially for a large-scaled simulation.

1.4.4 Influenza modeling in Thailand

To date, a few influenza models using Thailand data have been published.[7,64,78] The first one was conducted by Ferguson et al. which used agent-based models to simulate disease burden and effect of various control strategies at national scale. They assumed that a H5N1 pandemic influenza would occurred by re-assortment of avian virus and human virus, generating a virus with increased transmissibility. They seeded simulations with a single infection in the most rural third of the population (that is, with the lowest population density), assuming that rural populations are most likely to be exposed to the avian virus. This assumption is unrealistic if a new pandemic influenza originate from human influenza, which often start with crowded population. They simulated impact of targeted mass prophylactic use of antiviral drugs and reinforcements of other interventions aimed at reducing population contact rates to an antiviral-based containment policy. They reported that elimination of a pandemic may be feasible using a combination of geographically targeted prophylaxis and social distancing measures (school and workplace closure, quarantine zones in which movements in and out of the affected area are restricted). If the R_0 of the new virus is below 1.8, they predicted that a stockpile of 3 million courses of antiviral drugs should be sufficient for elimination.

The second study was conducted by Longini et al. They used a discrete-time stochastic simulation model of influenza spread within a structured geographically distributed population of 500,000 people to compare the effectiveness of various intervention strategies (antiviral

prophylaxis, H5N1 influenza vaccine, case quarantine) against a new strain of influenza that may originate from avian influenza. This study aimed to model effectiveness of those interventions only. Like the first study, this study is based on rural area context and was small scale model. This may not fit to a new pandemic influenza originate from human influenza. They reported that If the R_0 is below 1.8, an antiviral agent stockpile on the order of 100,000 to 1 million courses for treatment and prophylaxis would be sufficient to contain the outbreak. If pre-vaccination occurred, then targeted antiviral prophylaxis could be effective for containing strains with an R_0 as high as 2.1. Combinations of targeted antiviral prophylaxis, pre-vaccination, and quarantine could contain strains with an R_0 as high as 2.4.

The third study was conducted by Krumkamp et al. who used a deterministic SEIR model without age structure assuming a homogeneously mixing population at 2 provinces of Thailand to assess health resource gap for influenza treatment in a novel influenza A (H1N1) scenario. This study did not cover aspect of disease prevention and control. Also, assuming a homogeneously mixing population might not be true, especially for intervention policy and control strategies. They found the differences in health outcomes between a province with adequate resources and a province with potential resource gaps. The province with adequate resources had adequate hospital beds and medical ventilators for the outbreak response. Also the antiviral drugs stockpile was sufficient to treat all critical cases. However, the surplus did not allow for changing treatment strategies to provide to outpatients who had mild symptoms. For another province with resource gap, medical ventilators need to be increased by 27.3% of the number current available, and antiviral drugs stockpile must be more than doubled in order to treat all hospitalized influenza cases.

1.4.5 The Framework for Reconstructing Epidemic Dynamics (FRED)

In this study, a large-scale agent-based framework of infectious diseases, namely FRED and developed by the University of Pittsburgh Public Health Dynamics Laboratory (PHDL) in collaboration with the Pittsburgh Supercomputing Center (PSC) and the School of Computer Science at Carnegie Mellon University, was used. FRED is a freely available open-source epidemic modeling system that uses census-based synthetic populations to capture the demographic and geographic heterogeneities of the population, including realistic household, school, and workplace social networks.[79] Mitigation strategies in the framework include vaccination, anti-viral drugs, and school closure policies. FRED models are currently available for every state and county in the United States, and selected international locations. Public health planners can use FRED to explore the possible influenza epidemics and to help evaluate the likely effect of interventions.

FRED was designed as a flexible framework for epidemic modeling. While originally designed to study influenza, FRED can be adapted to other infectious diseases, by modifying configuration files characterizing the natural history of the disease. Other user-modifiable parameters include the initial immunological profile of the population, the availability and efficacy of vaccine and anti-viral drugs, and a flexible set of intervention policies regarding vaccine distribution, school closures and other non-pharmaceutical interventions. Disease parameters and assumptions followed the process described in study by Cooley et al.[80] and systematic review of Zhou et al.[81]

PHDL made significant additions to FRED (FRED/Thailand) to support particular simulations that were not available in existing FRED. These contributions included the addition of (1) hospital assignments for workplace, (2) identification of healthcare workers (HCWs), (3)

chronic medical conditions and pregnancy assignments for agents (4) hospital preference assignments for agents, (5) temporary hospitalization of agents, (6) face mask behaviors, (7) hand washing behavior; and getting FRED/Thailand to run efficiently on Blacklight at PSC.

1.4.6 Synthetic population

FRED explicitly represents every individual living in a specific geographic region. However, Thailand synthetic population was not available in existing synthetic population database of the Research Triangle Institute (RTI International). The investigators in this study in collaboration with RTI International had developed a new Thailand synthetic population. The synthetic population used an iterative fitting method[82] to generate an agent population from the aggregated census data. Thai census data (year 2000) on household size and age distributions were used to generate the synthesized agents and households.

School and workplace assignments followed the methods described by Cajka et al.[83] School data (year 2011) from the Thai Ministry of Education[84] on ≈38,000 schools were used to determine the distribution of school sizes, number and proportions of children in school as a function of age for school assignment. The schools assignment method was based on the assumption that students are enrolled at the closest school having adequate capacity. Data of Thailand Industrial census in year 2007[85] were used for workplace assignment. The data indicated numbers and percentages of workers by size of work place (1 - 15, 16 - 25, 26 - 30, 31 - 50, 51 - 200, and >200 workers). The locations (point) of workplaces were generated. Then, each non-school age synthetic individual was assigned to a workplace such that the distribution and capacity of each workplace was appropriate.

As original synthetic population did not have hospital assignment, the investigators in this study in collaboration with PHDL had created synthetic hospitals. The actual hospitals data of Thailand Ministry of Public Health in year 2013[86] were used to create synthetic hospitals. The method assumed that the number of HCWs who interact with patients was proportional to the number of beds by the value of 1 to 1 (e.g. a hospital with 100 beds would have 100 HCWs who interact with patients). The simulation then found a synthetic workplace with approximately the same number of employees and moved the assigned employees to work in the hospital as HCWs. To determine which hospital a family will visit, the method used a gravity model where the probability of going to a given hospital was determined by the (number of beds) / (distance from household to hospital)^2.

Each agent has associated with its demographic information (e.g., age, sex, etc.), health information (e.g., current health status, date of infection, level of symptoms, infectiousness, susceptibility, etc.), location for social activity (e.g., household, neighborhood, school or workplace, etc.), and health-related behaviors (e.g., probability of staying home when sick, probability of getting a vaccine, etc.).

1.5 INFLUENZA CONTROL MEASURES

Influenza control measures have goal to reduce the viral transmission, minimize morbidity and mortality. These interventions include influenza vaccines, antiviral agents, and non-pharmaceutical interventions.

1.5.1 Influenza vaccines

Vaccination is at present the primary public health intervention for the reduction of disease seasonal influenza. Vaccines protect against influenza by stimulating an antigen-specific immune response in recipients. However, the antigens contained in the vaccine must match those of the circulating virus to be effective at reducing influenza infection. So far, development of vaccine against a specific type of influenza virus and its production requires several months. As a result, if a vaccine does not match a circulating strain, it would take months to produce the new vaccine, and the peak will likely have passed when the vaccine is available.

Vaccination has both direct and indirect effects. Direct effects occur because the person who is vaccinated may have reduced risk of becoming infected. Indirect effects occur because someone who is vaccinated will have reduced risk of spreading the pathogen to others (in part because they have a reduced risk of becoming infected). Close contacts of this vaccinated person will therefore also have reduced risk of becoming infected even if they do not receive vaccine themselves.

Two types of influenza vaccines are available: trivalent inactivated influenza vaccines (TIV) and live attenuated influenza virus vaccine (LAIV).

The TTV vaccines are available for use among adults of all ages regardless of underlying medical conditions. Efficacy is from 70 to 90% in healthy adults younger than 65 years of age and 30–90% in children, with lower efficacy in younger children.[87] The LAIV is approved for use among healthy, non-pregnant adults through the age of 49. Efficacy is usually from 70% to 90%.[87]

These vaccine efficacy estimates are based on clinical trials, and usually be common lower efficacy in real world situations. Many factors may affect its efficacy. The vaccine is most effective if it contains a same antigenic strain with circulating influenza virus. However, there are yearly variability of influenza viral strains and vaccine manufacturing has about 1 year lag to justify vaccine antigenic strains and production. This does not assure that the current vaccine will contains exactly the same strains with current circulating virus. In addition, vaccine effectiveness in a population also depends on vaccine cold-chain and administration. Vaccines are temperature-sensitive biological products. The degradation rate of a vaccine is determined by the storage temperature: the higher the temperature, the more rapid and extensive is the degradation [88]. Influenza vaccine should be stored in the refrigerator at 35° to 46°F (2° to 8°C), aim for 40°F (4°C), and should not be frozen.

1.5.2 Antiviral agents

There are two classes of antiviral agents approved for the treatment and prophylaxis of influenza infections. The first class is M2 ion channel blockers; include Adamantanes, Amantadine and Rimantadine. The second class is neuraminidase inhibitors; include Oseltamivir and Zanamivir. For treatment purpose, both classes of drugs need to be administered within 48 hours of symptom onset to be effective.

Amantadine and Rimantadine should no longer be used for the treatment of influenza due to the high incidence of resistance. Resistance to Amantadine and Rimantadine is seen with a frequency of ≥50% in children,[36,89] the elderly and in immunocompromised patients.[90,91] Oseltamivir is the best choice for stockpiling given its efficacy,[92,93] even with some degree of resistance.[69]

Guidelines regarding antiviral drugs use are necessary because there is only a limited supply of drugs during a pandemic or epidemic. Government stockpile policies are designated primarily for treatment.

1.5.3 Non-pharmaceutical interventions

Various non-pharmaceutical intervention strategies are a first line of defense against outbreak of infectious diseases because they can be implemented rapidly. These types of interventions seek to reduce the contacts between individuals or disrupt a spread of pathogen. The interventions have include strategies such as social distancing measures (such as closing schools and childcare centers, closure of public places, limit mass transit, isolation and quarantine), and personal protection and hygiene measures (such as mask wearing and hand washing).

1.5.3.1 School closure

The rationale for school closure is that children are thought to be important vectors of transmission and more infectious, are more susceptible to most influenza strains than adults, and the high contact rates in schools favor transmission. School closure is associated with decreased morbidity from respiratory tract infections[94] including influenza.[95] It has been proposed as a method of reducing both the total number of influenza cases and peak of attack rate during

pandemic.[96] Epidemiological study using diseases surveillance data suggested that school holidays prevent 16–18% of seasonal influenza cases (18–21% in children); prolonged school closure during a pandemic might reduce the cumulative number of cases by 13–17% (18–23% in children) and peak attack rates by up to 39–45% (47–52% in children).[97] However, school closures result in significant economic impacts because caregivers have to leave the workforce to care for unattended-school children.[98,99] This make the school closure policy has a community controversial.

1.5.3.2 Isolation and quarantine

Isolation of the sick and quarantine of contacts measured in 1918 pandemic influenza was ineffective.[100] After physicians reported influenza case, the patients were quarantined and their houses were placarded. Many citizens regarded the placard as an injustice and avoided quarantine. Also, many physicians hesitated to report mild symptom patients as influenza case. This made quarantine measure ineffective.

Some of the lessons learned from the 2003 SARS epidemic can be applied to influenza; early isolation of patients and quarantine of contacts successfully interrupted SARS transmission. Influenza has a serial interval of 2 to 4 days and infectivity is maximal early in illness, whereas for SARS the serial interval is 8–10 days and infectivity peaks during week 2 of illness. These factors allow little time for instituting the isolation and quarantine interventions that were essential in controlling SARS.[101] However, Miyaki et al. conducted a study to evaluate quarantine measure for workplaces; asking workers whose family members developed an influenza-like illness (ILI) to stay at home voluntarily until 5 days had passed since the resolution of ILI symptoms or 2 days after alleviation of fever (The company paid full wages during this time). With 100% compliance to intervention, the waiting on full pay policy in the

workplace reduced the overall risk of influenza A H1N1 by about 20% in one influenza season.[102]

1.5.3.3 Personal protection and hygiene measures

Experience from previous influenza pandemic showed that wearing mask in public was ineffective. During the 1918 influenza pandemic, mask use was common and even required by law in many jurisdictions. However, the medical officer of health for Alberta, Canada, reported that cases of disease continued to increase after mask use was mandated.[100] Recently, a limited controlled study evaluated the efficacy of wearing mask in preventing transmission of influenza virus was initiated and results have yet to be published.

During the SARS epidemic in 2003, surveys conducted in Hong Kong between April and May 2003 showed that most of the population wore a face mask (76%). In this period, influenza virus isolation rates decreased. However, since multiple hygienic measures were implemented (such as hand washing, covered their mouths when sneezing or coughing, used diluted bleach for household cleaning), the contribution of mask wearing was unclear.[103] MacIntyre et al. conducted a prospective cluster-randomized trial comparing surgical masks, non-fit-tested P2 masks, and no masks in prevention of influenza-like illness (ILI) among household members of ILI patients. They reported that adherent use of P2 or surgical masks significantly reduces the risk for ILI infection, with a hazard ratio equal to 0.26 (95% CI 0.09 to 0.77; $p = 0.015$).[104] Effectiveness of face mask use by index influenza cases was questionable in one study. Canini et al. conducted a cluster randomized intervention trial to evaluate the effectiveness of face mask use by index cases for limiting influenza transmission by large droplets produced during coughing in households. The result did not show any significant difference in ILI proportion among household contacts between the intervention arm and the control arm, even with a good

adherence to the intervention. The multivariable adjusted odds ratio for the intervention arm compared to the control arm was 0.95 (95%CI 0.44 to 2.05, p = 0.90).[105]

Many controlled studies have shown a protective effect of hand hygiene in reducing upper respiratory infections.[106-112] Luby et al. conducted a randomized controlled trial to assess the effect of hand washing promotion with soap on the incidence of acute respiratory infection and found that children younger than 5 years in households that received plain soap and hand washing promotion had a 50% lower incidence of pneumonia than controls (95% CI 34% to 65%).[107] Mater et al. evaluated the effect of a scheduled hand-washing program in elementary school children on absenteeism due to acute communicable illness and found that respiratory illness was reduced at 21%(95%CI 0.02% to 0.39%).[110] Talaat et al. studied the effectiveness of an intensive hand hygiene campaign (washing hands using soap and water at least twice during the school day for ≈45 seconds, followed by proper rinsing and drying with a clean cloth towel) on reducing absenteeism caused by ILI and laboratory-confirmed influenza and reported that overall absences caused by ILI and laboratory-confirmed influenza were reduced by 40% and 50%, respectively ($p<0.0001$ for each illness).[111] Stebbins et al. conducted a cluster-randomized trial in 10 elementary schools to assess efficacy of respiratory hygiene education and the regular use of hand sanitizer to reduce the laboratory-confirmed influenza. The interventions did not reduce total laboratory-confirmed influenza (A and B). However, the interventions did reduce school total absence episodes by 26% and laboratory-confirmed influenza A infections by 52%.[112]

In contrast, some studies showed no protective effect of face mask use alone or hand washing alone on ILI or influenza, but revealed effectiveness of both interventions combined.[113,114] Aiello et al. observed significant reductions in ILI during weeks 4–6 in the mask

and hand hygiene group, compared with the control group, ranging from 35% (95%CI 9% to 53%) to 51% (95%CI 13% to 73%), after adjusting for vaccination and other covariates. However, adherence to the interventions varied and there was contamination between groups, with noncompliance in the intervention group and some practicing the intervention in the control group.[113] Cowling et al. reported that effect attributable to fewer infections among participants using facemasks plus hand hygiene was OR= 0.33 (95%CI 0.13 to 0.87).[114]

1.6 SUMMARY

There are 3 types of influenza virus: A, B and C. Only influenza A is associated with widespread epidemics and pandemics. Influenza is generally seasonal in temperate climate zones but is less pronounced in tropical zones. Mechanisms contribute to influenza seasonality remain unclear. Some mechanisms have been proposed to explain the seasonality including contact rates, virus survival, and host immunity. Populations at risk for influenza are children, elderly, healthcare workers, people with chronic medical conditions, and pregnant women.

Mathematical and computational simulation models are being increasingly used to estimated a burden and evaluate impact of control strategies of influenza. One important disease transmission parameter is R_0. However, this number was often estimated using developed countries data.

Most models of influenza utilize compartmental models. A few studies have used agent-based simulation models than can take into account heterogeneity in population.

Several control measures can be implemented to prevent and control influenza. These intervention include vaccination, antiviral treatment and prophylaxis, non-pharmaceutical interventions (such as school closure, isolation, face mask wearing, and hand washing). Vaccination and antiviral prophylaxis have clear evidences of their efficacy, but has resource limitations on large-scale use in developing country like Thailand. Optimal influenza vaccine allocation simulations showed great benefit if is prioritized to children and elderly. However, there is no model assessing impact of vaccine prioritization to other risk population such as healthcare workers and people with chronic medical conditions. Some non-pharmaceutical interventions such as school closure and case isolation were often assessed for their impact and

have agreement on their effectiveness. However, a few study assess impact of face mask wearing and hand washing.

There are some questions need to be answered: what is R_0 estimate base on Thai population's context, how vaccine allocation policy affect influenza burden if it is prioritized to other risk population (healthcare workers and people with chronic medical conditions), are face mask wearing and hand washing effective on influenza control.

This study used agent-based model to estimated influenza burden in Thailand and assess impact of vaccine allocation policy and non-pharmaceutical interventions (mask wearing and hand washing). This study did not simulate effect of antiviral prophylaxis as this is not Thailand policy and its effectiveness was well documentation in other model studies.

The FRED was used to run simulation on Blacklight at PSC. A new synthetic Thai population with hospital assignment was developed for this study.

2.0 MANUSCRIPT 1: TRANSMISSIBILITY AND BURDEN OF INFLUENZA IN THAILAND

Manuscript in preparation

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2.1 ABSTRACT

Many studies of influenza modeling have estimated basic reproductive number (R_0) using previous influenza pandemics in developed countries. The R_0 based on Thailand's context is unknown and should be estimated for further studies of influenza dynamics and burden which may lead to better health resources allocation. Numbers of influenza case by week were obtained to estimate epidemic growth rate (r). The R_0 was estimated using formula relating the r and generation time. The projection of influenza burden was studied by fitting an agent-based computer simulation model. The model containing a 58,354,744 synthetic Thai population. At start, 100 agents were randomly assigned for initial infection. The model simulated the interactions of individuals with others at household, school and workplace over 120 days. The R_0 estimates ranged from 1.11 to 1.77 (median 1.39). For a R_0 = 1.4 and no any intervention, the overall attack rate was estimated to be 49.9% (symptomatic attack rate 33.4%). Incidence rates began rising at week 4th (0.05%), peaked at week 9th (10.5%), and subsided at week 17th (0.05%). During the same period simulation, Thailand had reported influenza cases with attack rate 0.04%. For R_0s equal 1.2, 1.6, 1.8 and 2.0; overall attack rates were 37.1%, 58.8%, 65.9%, and 71.7% respectively. The estimated Thailand R_0 is comparable to R_0 of developed countries. The results reveal that Thailand's surveillance report may have underestimated influenza's incidence. Effective control measures should be taken place within the first two weeks of outbreak to minimize number of cases.

Key words: Reproductive number, Influenza, Thailand, Computer simulation

2.2 INTRODUCTION

The important parameters for understanding disease transmission are the basic reproductive number (R_0) and serial interval.[115] The R_0 is defined as the average number of secondary infections created from a primary infection in an entirely susceptible population. If R_0 is greater than one, the disease has the potential to spread. If it is less than one, the disease will die out after only a few generations. The next influenza pandemic will start when a novel strain of influenza evolves with $R_0 > 1$ in humans. Control strategies are typically targeted to drive this number below one and maintain it there, as this will lead to eventual extinction of the epidemic.

Many modeling studies have estimated R_0 either from previous influenza pandemics or seasonal influenza. The estimated influenza R_0 range from 1.2 to 3.75.[51-59] Most of these studied used epidemiologic data from previous influenza pandemic years. However, the R_0 in seasonal years is relatively scarce. In addition, even when the information is available the most common countries studied were developed countries such as Switzerland, USA, England and Canada.[51-53,56,57] There have been a few studies about the transmissibility in developing countries, one in Brazil,[54] another in Mexico.[59] There is limited knowledge of R_0 in developing countries in Asia including Thailand.

Thailand may have difference social contacts and lifestyles compare to developed countries, or developing countries in South America. The R_0 based on Thailand's context should be estimated and used to further studies of influenza dynamics and control strategies.

In the case of seasonal influenza, it is less likely that people are entirely susceptible. A fraction of individuals may be effectively protected against infection, because of residual immunity from previous exposure to influenza or vaccination. So, a more practical quantity is an effective reproductive number (R_t), which is defined as the number of secondary infections that

arise from a typical primary case. Nevertheless, R_t can be approximate to R_0, especially when a proportion of immune individual is small.

The government of Thailand needs to understand the role of influenza in Thailand for policy planning purposes. Thailand-specific influenza R_0 can be used to estimate burden of influenza. This may lead to better health resources allocation and influenza preparedness.

This study will focus at human influenza strains that spread widely. We aim to estimate R_t of seasonal influenza, and model influenza to address the burden of disease in Thailand.

2.3 METHODS

2.3.1 Influenza R_t estimation

Influenza cases surveillance of the National Notifiable Disease Report was used to obtain influenza incidence. Bangkok, the capital city of Thailand, was selected as a sample for influenza incidence because there were outbreak every year and is a high risk area to spread influenza to other provinces. Bangkok is the biggest tourist city in Thailand and has crowded population. Bangkok has 5.6 million population. Approximately 36 million tourists (both Thais and foreigners) annually travel to Bangkok.

The numbers of influenza cases by week from 2003 to 2012 were obtained. An epidemic curve with logarithm scale for each year was plotted. Linear increase in cases on a logarithmic scale indicates exponential increase in the number of cases. The epidemic growth rate (r) was estimated during this exponential growth phase using the formula relating the number of cases(I)

at two time points t_1 (start) and t_2 (stop) of the growth phase. The calculated r per week was divided by 7 to obtain daily value.

$$r = \frac{1}{t_2 - t_1} ln\left(\frac{I(t_2)}{I(t_1)}\right)$$

The generation time (T_g) was estimated at 2.6 days.[7] The R_t was estimated using formula relating the epidemic growth rate and generation time.[7,116]

$$R_t = 1 + rT_g$$

2.3.2 Modeling influenza burden of Thailand

Synthetic population data

A synthetic population (with school and workplace assignments) of Thailand was developed by the Research Triangle Institute (RTI International).[83] In summary, RTI International used a proportional iterative method[82] to generate an agent population from aggregated census data. Thai census data (year 2000) on household size and age distributions were used to generate the synthesized agents and households. Each agent had a set of socio-demographic characteristics that included age, sex, employment status, occupation, and household location. School data (year 2011) from the Thai Ministry of Education[84] on ≈38,000 schools were used to determine the distribution of school sizes, number and proportions of children in school as a function of age for school assignment. The schools assignment method was based on the assumption that students are enrolled at the closest school having adequate capacity. Data of Thailand Industrial census in year 2007[85] were used for workplace assignment. The data indicated numbers and percentages of workers by size of work place (1 - 15, 16 - 25, 26 - 30, 31 - 50, 51 - 200, and >200 workers). The locations (point) of workplaces were generated. Then, each non-school age synthetic individual

was assigned to a workplace such that the distribution and capacity of each workplace was appropriate. Agents move among their households, assigned workplaces (for employed adults), schools (for school-aged children) and various locations in the community, where they interact with other agents who were household members, workplace mate, and classmate.

Disease and model parameterization

Disease parameters and assumptions follow the process described in a study by Cooley et al.[80] and systematic review of Zhou et al.[81] Individuals are classified according to their infection and immune status as either susceptible (S), latent or exposed (E), infectious (I), or recovered (R). All individuals are initially susceptible to influenza until infectious individuals are introduced into the model. Each newly infected individual enter a latent state. During this time, the agent is infected but not yet infectious to others. We assume that infectiousness and symptoms begin at the same time as the viruses are shed via droplets produced when infected people cough or sneeze. Thus latent period (the time from infection to when a host is able to transmit the pathogen) was approximate to incubation period. Then, the agent moves to the infectious state, in which the agent may infect others. Two-third of infected individuals develop symptoms.[64,76,117] Finally, the individual enters the recovered state and remains immune to subsequent infections.

The projection of influenza burden was studied by fitting an agent-based computer simulation model (ABM). This study used a Framework for Reconstructing Epidemiological Dynamics (FRED) for modeling. FRED is an open source, modeling system developed by the University of Pittsburgh Public Health Dynamics Laboratory in collaboration with the Pittsburgh Supercomputing Center (PSU) and the School of Computer Science at Carnegie Mellon University.[79] The model is a stochastic, spatially structured, individual-based discrete time simulation. Individuals are co-located in households, with households being constructed to

reflect typical generational structure while matching empirical distributions of age structure and household size for Thailand.

The probability that an infected individual transmits influenza to susceptible persons depended on the rate of potentially infectious contacts, and the probability per contact of transmitting influenza. Every susceptible individual who contacts an infectious individuals had a probability of disease transmission (per contact), derived from prior studies of the 1957–1958 Asian influenza pandemic.[7,64,76] As in Cooley et al.[80], we assumed that 50% of sick individual stay at home and do not interact with any agents outside of the household. Additionally, we assume that all community contacts increase by 50% on weekends. The model was calibrated using the Ferguson et al. approach from historical (1957–1958, 1968–1969) influenza pandemics.[7] We specifically used the 30–70 rule developed in which 30% of all transmission occurred in the household and 70% of all transmission occurred outside the household (33% in the general community, and 37% in schools and workplaces).[7] The strategy was to estimate mean contact rate per day at each location that produced and epidemic that satisfied the 30-70 rule calibration criteria. To achieve this rule, within household contacts were treated differently than other locations. We assumed that each pair of agents within a household make contact each day with a specified probability. This probability is tunes as part of the calibration step to achieve the 30-70 target distribution. At the start of each simulation, 100 agents were randomly assigned for initial infection. The individuals interact daily with others in the same household, school and workplace with a fixed mean number of people that they contact per day (from calibration step). The simulations were run over 120 days. Each presented result is the average of 10 simulation runs for one experiment (one R_0 value).

Computational specifics

Simulations were performed on Blacklight at PSU. Blacklight is an SGI servers, clusters and supercomputers, shared-memory system comprising 256 blades. Each blade holds 2 Intel Xeon X7560 (Nehalem) eight-core processors, for a total of 4096 cores across the whole machine. Each core has a clock rate of 2.27 GHz. Each experiment (10 simulation runs in parallel) is run using parallel computing over 16 computer nodes, taking an average of 3.5 hours on each experiment (17.5 hours of total computer time).

2.4 RESULT

2.4.1 Influenza R_t estimation

From 2003 to 2012 influenza incidence throughout the year with multiple peaks between year 2003 - 2008 and observed prominent peak between year 2009 – 2012 were reported in Bangkok. The number of reported cases by year ranged from 914 cases in year 2003 to 4,195 cases in 2008. The reported cases increased to 19,185 and 22,387 cases in year 2009 and 2010, respectively. The number of cases declined slightly to 14,335 and 16,639 cases in year 2011 and 2012, respectively. The highest incidence was usually identified during the rainy season (June to September). Epidemic curves were ploted to identify the highest linear increase in cases on a logarithmic scale. The annual epidemic growth rates ranged from 0.042 to 0.297 per day and the annual R_t estimations ranged from 1.11 to 1.77 (median 1.39) (Table 6). If data between year 2010 - 2012 were excluded, The R_t estimations ranged from 1.3 to 1.77 (median 1.49). Based on

these R_t values with median 1.39 and R_t can be approximate to R_0, R_0 was estimated to 1.4 for further influenza modeling.

2.4.2 Modeling influenza burden of Thailand

A synthetic population size of 58,354,744 was created to represent Thai population. We considered the scenario that no any intervention to control influenza transmission and assume influenza R_0 = 1.4. When 100 randomly infected individuals were introduced, incidence of infection gradually increased and peaked on day 59 (Figure 7). At the end of day 120, there were 29,120,708 cumulative new infected individuals. The overall attack rate was estimated to be 49.9% (Figure 8). Of all infection, 19,509,482 infected individuals were symptomatic case. Symptomatic attack rate was 33.4%. The simulation showed that 56.1% of infected individuals were adult, followed by children age <12 years old (24.7%), adolescent age 12-18 years old (14.7%) and elderly (4.5%) respectively. Incidence by week ranged from 0.55 to 11,118.11 per 100,000 population (Table 7). Incidence rates began rising at week 4 (0.05%), peaked at week 9 (10.5%), and subsided at week 17 (0.05%) (Figure 9).

We compared the influenza incidence of the simulation study to reported influenza case from the Thailand Notifiable Disease Report. The report is hospital-based passive surveillance; mostly is governmental hospitals, clinical diagnosis with some laboratory confirmation. During the same period simulation, Thailand had reported influenza cases with attack rate 0.04%, while the simulation showed symptomatic attack rate was 33.4%.

Accounting for uncertainty of R_0, we modeled influenza incidence with R_0 ranged 1.2 - 2.0. The higher R_0, the higher overall attack rate. For R_0s equal 1.2, 1.4, 1.6, 1.8 and 2.0; overall attack rates were 37.1%, 49.9%, 58.8%, 65.9%, and 71.7% respectively. The lowest R_0 (1.2),

attack rate began rising at week 5 and peaked at the end of simulation, week 17. For R_0 between 2.0 and 1.6, attack rate began rising around week 2 - 3 and peaked around week 6 - 8 (Figure 10).

2.5 DISCUSSION

It is known that R_t is always less than R_0 because not everyone is susceptible at beginning of outbreak due to a vaccination or prior infection. However, protective immunity to influenza virus often decline after vaccination or infection. The immunity is quite strain specific, but influenza viruses are constantly changing. In addition, influenza vaccine was not widely used in Thailand before 2010. So, R_t should be properly approximate to R_0. R_t median in this study is based on situation that no or low level of immunity in population, similar to other pandemic R_0.

R_t values after 2010 were a little lower than before 2010. This might be a result of vaccine program. However, if R_t values after 2010 were excluded, the median R_t would be 1.49 and did not change much from original estimation. Our study showed that the estimated Thailand influenza R_t is lower than previous influenza pandemics,[51-56] is comparable to the range of those estimated seasonal influenza R_0 from developed countries[58] and is similar to R_0 of pandemic influenza A(H1N1) either in Thailand[118] or other countries.[59,119] This finding is in close agreement with a prior study which used a R_0 from 1.4 - 1.5 to model influenza in Thailand.[7]

The increasing number of reported influenza cases between 2009-2012 is due to outbreak of pandemic influenza A(H1N1) and a strengthening of the surveillance system. Unfortunately, the surveillance system had no information to separate pandemic influenza cases form seasonal influenza cases. This was less likely to affect R_t estimation, as R_0 of pandemic influenza approach to R_0 of seasonal influenza. Also, when we exclude data between 2010 - 2012, the

estimated R_t did not change much. After 2009, the influenza vaccine was more available. This increased a proportion of immune individuals and resulted in decline of estimated R_t in later years.

This is a second national scale simulation of influenza in Thailand. This study reported a higher attack rate than the previous study (49.9% versus 33%).[7] Our study randomly seeded 100 infected individuals at beginning as we aimed to model human seasonal influenza that typically occur throughout the country, while the previous model seeded 1 infected individual in the rural population as an assumption of reassortment of avian virus and human virus. The incidence in our model was markedly higher than reported case in surveillance. There were several explanations; (1) majority of influenza had mild symptoms, they might seek self-medication and did not visit healthcare facilities, or visited hospital but were diagnosed to be common cold or flu-liked illness that will not be reported to the surveillance, (2) the surveillance was under-report,[120] (3) limitation of the surveillance that mainly based on clinical diagnosis and collected data only from governmental hospitals, (4) there was an effect of some protective interventions in population such as vaccination, personal protection and hygiene. Since 2010, influenza vaccine became more available but is provided only in some population at risk and has limited amount. Also, personal protection was not well practiced in general population. So, the finding reveal that Thailand's surveillance report may have underestimated influenza's incidence. Case-based surveillance usually represented the tip of iceberg phenomenon. There was high rate of asymptomatic infection and most symptomatic cases were self-managing without medical consultation.[121]

We observed four weeks period before rising of incidence. This is too short period for vaccination after an outbreak occurs, as the influenza vaccine takes about two weeks after

vaccination for antibodies to develop in the body and provide protection against influenza virus infection. The proper strains of influenza vaccine should be identified before the influenza season and vaccination should occur prior to the start of the influenza season. During the influenza season effective control measures should be implemented to minimize number of cases. Non pharmaceutical interventions (such as mask wearing, hand washing) may be recommended. Antiviral prophylaxis may be alternative intervention but needs high medication resource and risks to drug resistance for treatment.

This study has some strengths. We used Thailand-specific R_0 to model influenza burden. Even the R_0 does not differ from literature, we have more confidence that influenza transmission in the model represent to influenza dynamic in Thailand. We conducted a national-scale study which epidemiological studies may be difficult to perform. This allows us to estimate influenza incidence of the country, especially when asymptomatic infection play some role in disease transmission. Our study has some limitations. We assumed no immunity or any intervention. This made the simulation had higher attack rate than reality. However, the model can be used as baseline for no-intervention scenario, and add other interventions in further simulation to measure their effectiveness. The model did not take into account long distance travelling. This may increase time of disease's spread, but this is not a major concern as we randomly seeded 100 infected individuals at beginning. They spread to the whole country and should account for long distance travelling. Because of the computational costs involved, the current results do not include a sensitivity analysis that involved the underlying transmission parameters.

In conclusion, the estimated Thailand R_t is comparable to R_0 of developed countries. Influenza burden may be under recognized in Thailand. Modeling is a tool to provide decision makers with information for influenza preparedness and control.

Acknowledgments

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2.6 TABLES

Table 6 The epidemic growth and R_0 estimation between year 2003 - 2012

Year	Epidemic growth rate (per day)	R_t	Predominant subtype in Thailand *
2012	0.051	1.13	B
2011	0.042	1.10	A/H3
2010	0.044	1.11	A/H1 pandemic 2009
2009	0.189	1.49	A/H1 pandemic 2009
2008	0.255	1.66	B
2007	0.141	1.36	A/H3
2006	0.117	1.30	A/H1
2005	0.297	1.77	A.H3
2004	0.224	1.58	Not available
2003	0.156	1.40	Not available

* Source: Influenza virological surveillance, the Thailand National Institute of Health (NIH)

Table 7 Incidence of influenza by week

Week	Incidence per 100,000 population
1	0.55
2	2.36
3	10.80
4	49.96
5	227.36
6	952.49
7	3,259.12
8	7,696.79
9	11,118.11
10	10,520.85
11	7,589.19
12	4,504.02
13	2,282.74
14	1,048.06
15	430.92
16	151.13
17	48.34
18	10.11

2.7 FIGURES

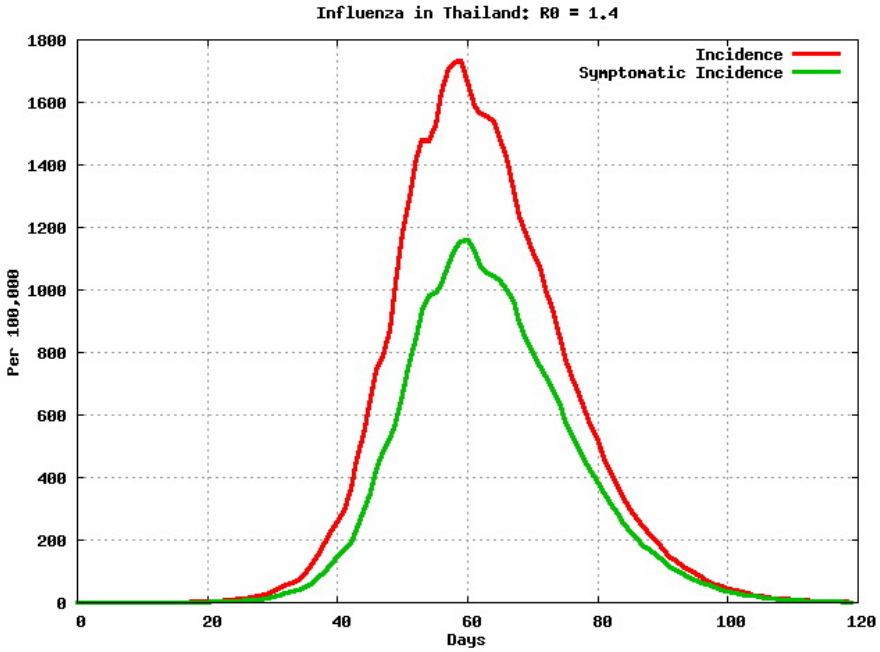

Figure 7 Daily incidence of influenza infection for R_0 = 1.4 in the absence of control measures

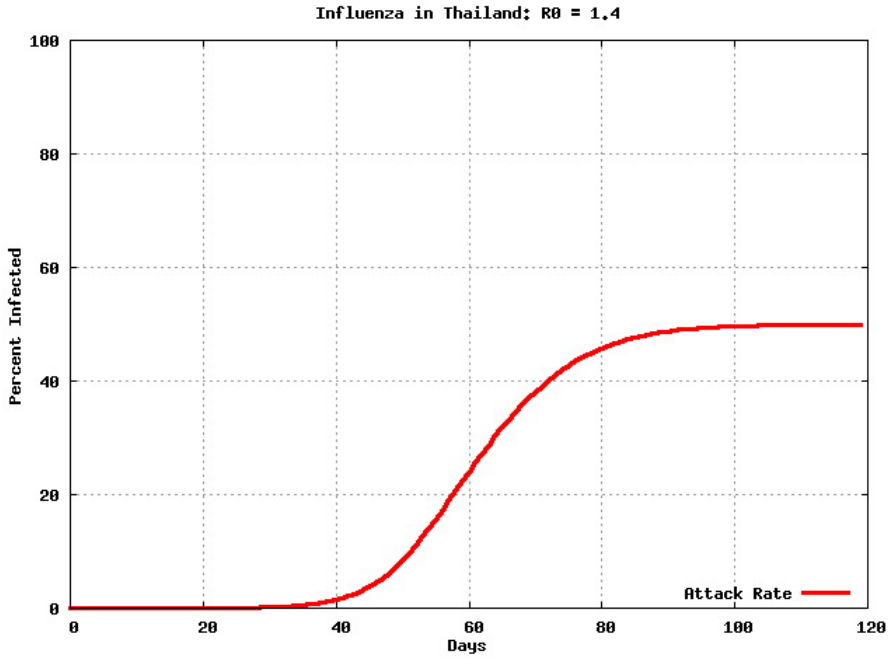

Figure 8 Overall attack rate (all infection) of influenza

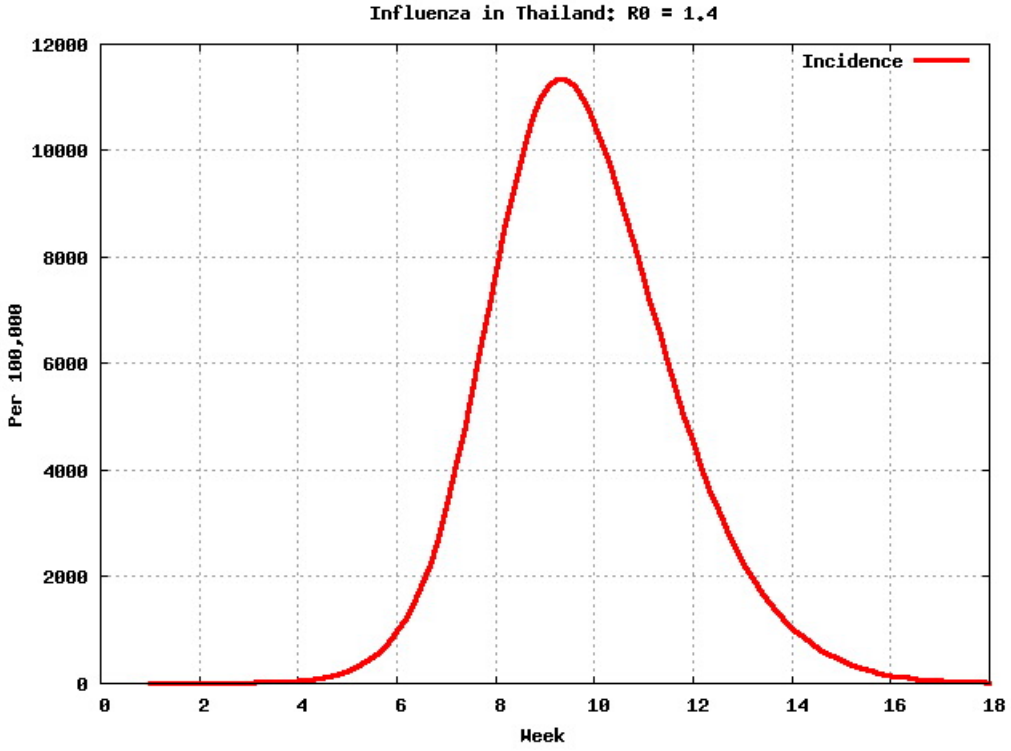

Figure 9 Attack rate (%) of influenza by week

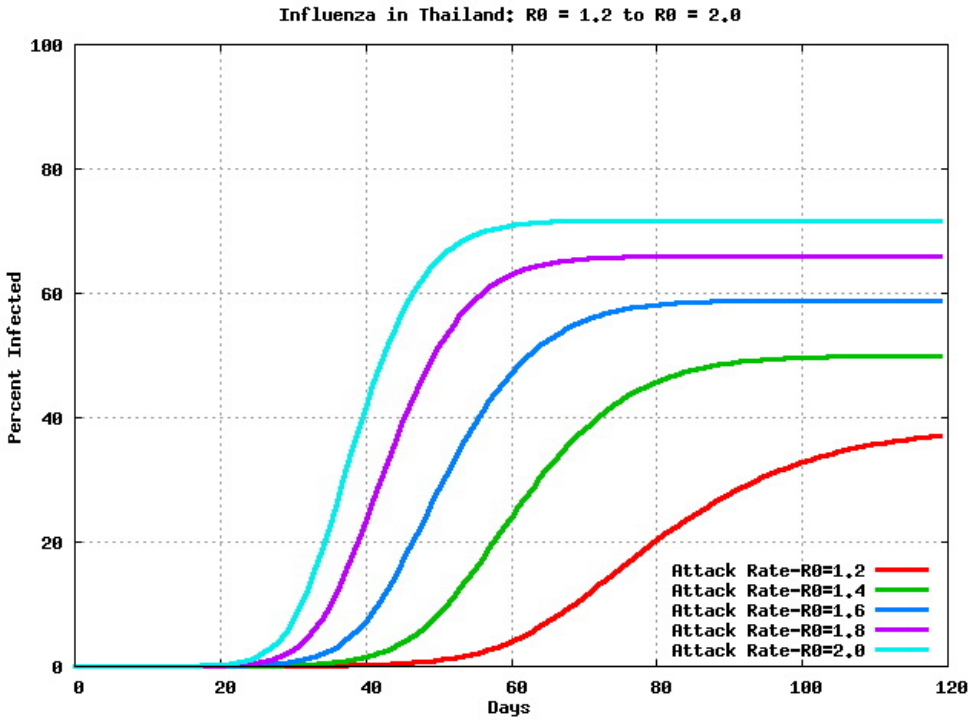

Figure 10 Incidence of influenza infection over time by R_0 in the absence of control measures

3.0 MANUSCRIPT 2: OPTIMIZING INFLUENZA VACCINE PRIORITIZATION IN THAILAND

Manuscript in preparation

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3.1 ABSTRACT

Many studies reported that influenza vaccination was associated with reduction in hospitalization or death from influenza in both healthy and at-risk medical conditions. Thailand has a current vaccine policy targets at healthcare worker (HCWs), people aged 6-24 months or ≥65 years, people with chronic medical condition (CMC), and pregnant women. However, with a limited resource, information of optimizing vaccine allocation is needed. The projection of influenza burden was studied by fitting an agent-based computer simulation model. The model contains a 58,354,744 synthetic Thai population, incorporates people with CMC and HCWs. At start, 100 agents were randomly assigned for initial infection. The model simulated the interactions of individuals with others at household, school, workplace, and hospitals over 180 days. Impacts of influenza vaccine on morbidity and mortality were simulated at 50%, 75% and 100% coverage. The highest attack rate occurs in school-age children and adolescent (15.32%). 100% coverage of target population policy can avoid morbidity and mortality by 47.06% and 59.61% in total population respectively. However, the benefit is very small for HCWs (3.75% case reduction). The most extended policy to include children aged 2-18 years old can avoid >99% of cases. Decrement of vaccine coverage from 100% to 75% and 50% coverage has much impact on both target population and target population plus children 2-5 years old vaccine policy. Extended policy to vaccinate preschool and school-aged children is optimizing strategy. Vaccination alone may not prevent influenza outbreak in healthcare settings. Modeling is a tool to provide decision makers with information for influenza preparedness and control.

Key words: Influenza, Vaccine, Thailand, Computer simulation

3.2 INTRODUCTION

Vaccination is the principle strategy for reducing the disease burden of many infectious diseases such as polio, diphtheria, pertussis, tetanus, measles, rubella, and mumps. Vaccination has both direct and indirect effects. Direct effects occur because the person who is vaccinated may have reduced risk of becoming infected. In addition, it has the indirect benefit of decreasing transmission of the disease, thereby reducing the infection risk even for those who have not been vaccinated.

Influenza vaccination has been an effective intervention against influenza in developed countries. For example, influenza vaccination in the United States has long been recommended for all elderly, younger children, pregnant women, persons who have chronic medical conditions, with the recent expansion of recommendations to include all children up to age 18 years.[122] Influenza vaccine can prevent influenza-specific illness by 70% to 90% in healthy adults and 30% to 90% in children.[87] Retrospective cohort studies have shown a surprisingly large protective effect of influenza vaccination against deaths from any cause, especially among elderly.[123-125] These studies consistently reported that influenza vaccination was associated with reduction in hospitalization or death for pneumonia, influenza, all respiratory conditions, cardiac diseases and stroke in both healthy and at-risk medical conditions.

The impact of influenza vaccine is greater in persons with high-risk medical groups. Influenza vaccination is most effective when circulating viruses are well-matched with vaccine viruses. However, influenza viruses are constantly changing, and the vaccine will not prevent disease from other strains of influenza viruses not contained in the vaccine. Each year scientists try to match the viruses in the vaccine to those most likely to cause flu that year. So annual vaccination is recommended.

Thailand has a policy to use influenza vaccine to prevent and control influenza outbreak. However, with a limited resource, information of optimizing vaccine allocation is needed to guide the policy. The general problem is how to choose groups of the population that should receive priority in getting the intervention. In 2013, Thailand Ministry of Public Health recommended that the following groups should have higher priority to receive the seasonal influenza vaccine based primarily on their occupational risk to transmit influenza, increased risk of infection or experiencing more severe influenza-related disease complications: (1) healthcare, outbreak investigation and laboratory personnel, (2) persons aged 2 through 65 years who have health conditions associated with higher risk of medical complications from influenza, (3) all persons aged $\geq$ 65 years, (4) all children from 6 months through 2 years of age, (5) pregnant women with gestational age $\geq$ 4 months, (6) persons with mental retardation, (7) persons with thalassemia or immuno-compromised, (8) obese people (body weight > 100 Kg or body mass index > 35 Kg/m^2). However, vaccine supply may be limited and may not cover 100% of the target population.

As a result some key questions need to be answered: which sub-group should receive greatest priority, and how strictly (or vaccine coverage) should this recommendation be adhered to prioritized group. The evaluation of vaccination policies for their implementation is essential to allocate resources and to minimize disease burden. This study has aim to address the potential benefit on various vaccine allocation scenarios in a limited resource situation.

3.3 METHODS

Synthetic population data

A synthetic population (with school and workplace assignments) of Thailand was developed by the Research Triangle Institute (RTI International).[83] In summary, RTI International used a proportional iterative method[82] to generate an agent population from census aggregated data. Thai census data (year 2000) on household size and age distributions were used to generate the synthesized agents and households. Each agent had a set of socio-demographic characteristics that included age, sex, employment status, occupation, and household location. School data (year 2011) from the Thai Ministry of Education[84] on ≈38,000 schools were used to determine the distribution of school sizes, number and proportions of children in school as a function of age for school assignment. The schools assignment method was based on the assumption that students are enrolled at the closest school having adequate capacity. Data of Thailand Industrial census in year 2007[85] were used for workplace assignment. The data indicated numbers and percentages of workers by size of work place (1 - 15, 16 - 25, 26 - 30, 31 - 50, 51 - 200, and >200 workers). The locations of workplaces were generated. Then, each non-school age population was assigned to a workplace such that the distribution and capacity of each workplace was appropriate.

We used data of the actual hospitals in Thailand[86] to create synthetic hospitals with estimated number of HCWs. The method assumed that the number of HCWs who interact with patients was proportional to the number of beds by the value of 1 to 1 (e.g. a hospital with 100 beds would have 100 HCWs who interact with patients). The simulation then found a synthetic workplace with approximately the same number of employees and moved the assigned employees to work in the hospital as healthcare workers (HCWs). To determine which hospital a

family will visit, we used a gravity model where the probability of going to a given hospital was determined by the (number of beds) / (distance from household to hospital)^2.

We randomly assigned synthetic population to had chronic medical condition (CMC) based on the 4th National Health Examination Survey of Thailand (year 2008 - 2009). The survey reported that among people age > 15 years old, prevalence of asthma was 3%, chronic obstructive pulmonary disease (COPD) was 0.4%, chronic renal disease was 0.8%, diabetes was 6.9%, and coronary heart disease (CHD) was 1.4%. Prevalence of diabetes and CHD was stratified by age group. The point prevalence of pregnant women was estimated from average of age-specific fertility rate year 2002 - 2011. We assumed people with CMC will visit hospital once a month for disease follow up and getting drugs.

Agents move among their households, assigned workplaces or hospitals (for employed adults), schools (for school-aged children) and various locations in the community, where they interact with other agents who were household members, workplace mate, and classmate.

Disease and model parameterization

Disease parameters and assumptions followed the process described in study by Cooley et al.[80] and systematic review of Zhou et al.[81] Individuals are classified according to theirs infection and immune status as either susceptible (S), latent or exposed (E), infectious (I), or recovered (R). All individuals are initially susceptible to influenza until infectious individuals are introduced into the model. Each newly infected individual entered a latent state. During this time, the agent was infected but not yet infectious to others. We assumed that infectiousness and symptoms began at the same time as the viruses are shed via droplets produced when infected people cough or sneeze. Thus latent period (the time from infection to when a host is able to transmit the pathogen) was approximate to incubation period. Then, the agent moves to the infectious state, in

which the agent may infect others. Two-third of infected agents develop symptoms.[64,76,117] Finally, the agent enters the recovered state and remains immune to subsequent infections.

We assumed the following base probability values for hospitalization, outpatient-care and case fatality: outpatient-care probability = 0.88,[126] hospitalization probability = 0.22 (from database of Thailand Notifiable Disease Report, that was a proportion of inpatient among reported influenza cases), case fatality probability = 0.0000715.[127] Risk factors for severe outcomes following pandemic influenza A (H1N1) infection are similar to those for seasonal influenza.[128] We applied risk ratios of hospitalization or death from Van Kerkhove et al.[128] to those influenza cases who had chronic medical condition(s) or pregnancy in our simulations. We assumed that if an agent is hospitalized, then others in their household may visit them with a probability of 0.25 on each day that they remain hospitalized.

The projection of influenza burden was studied by fitting an agent-based computer simulation model (ABM). This study used a Framework for Reconstructing Epidemiological Dynamics (FRED) for modeling. FRED is an open source, modeling system developed by the University of Pittsburgh Public Health Dynamics Laboratory in collaboration with the Pittsburgh Supercomputing Center (PSU) and the School of Computer Science at Carnegie Mellon University.[79] The model was a stochastic, spatially structured, individual-based discrete time simulation. Individuals are co-located in households, with households being constructed to reflect typical generational structure while matching empirical distributions of age structure and household size for Thailand.

The probability that an infected agent transmitted influenza to susceptible agent depended on the rate of potentially infectious contacts, and the probability per contact of transmitting influenza. Every susceptible agent who contacted an infectious agents had a probability of

disease transmission (per contact), derived from prior studies of the 1957–1958 Asian influenza pandemic.[7,64,76] As in Cooley et al.[80], we assumed that 50% of sick agents stay at home and do not interact with any agents outside of the household. Additionally, we assumed that all community contacts increase by 50% on weekends. The model was calibrated using the Ferguson et al. approach from historical (1957–1958, 1968–1969) influenza pandemics.[7] We specifically used the 30–70 rule developed in which 30% of all transmission occurred in the household and 70% of all transmission occurred outside the household (33% in the general community, and 37% in schools and workplaces).[7] The strategy was to estimate mean contact rate per day at each location that produced and epidemic that satisfied the 30-70 rule calibration criteria. To achieve this rule, within household contacts were treated differently than other locations. We assumed that each pair of agents within a household make contact each day with a specified probability. This probability is tunes as part of the calibration step to achieve the 30-70 target distribution. At the start of each simulation, 100 agents were randomly assigned for initial infection. The individuals interact daily with others in the same household, school and workplace with a fixed mean number of people that they contact per day (from calibration step). We considered influenza R_0 = 1.4. The simulations were run over 180 days. Each presented result is the average of 7 simulation runs for one experiment (one vaccine strategy).

Vaccine efficacy and vaccine strategies

We assumed a vaccine efficacy by age groups as follows: children age 6 months to 18 years old is 0.62 [129], adults age 19 to 64 years old is 0.73 [130], adults age 65 and over is 0.58 [131]. We assumed that individuals are vaccinated at a sufficient time prior to the epidemic to allow for full immunity to develop (base on its efficacy). Five vaccine policy schemes were modeled: (1) no vaccination, (2) 100% vaccination coverage in the entire Thai population, (3) 100% vaccination

coverage in the target population (healthcare personnel, persons who have chronic health conditions, all persons aged ≥ 65 years, all children from 6 months through 2 years of age, pregnant women), (4) 100% vaccination coverage in the target population plus children age 2 to 5 years old, (5) 100% vaccination coverage in the target population plus children age 2 to 18 years old. We also repeated vaccine strategies with both 50% and 75% vaccine coverage.

Computational specifics

Simulations were performed on Blacklight at PSU. Blacklight is an SGI servers, clusters and supercomputers, shared-memory system comprising 256 blades. Each blade holds 2 Intel Xeon X7560 (Nehalem) eight-core processors, for a total of 4096 cores across the whole machine. Each core has a clock rate of 2.27 GHz. Each experiment (7 simulation runs in parallel) is run using parallel computing over 16 computer nodes, taking an average of 8 hours on each experiment (104 hours of total computer time).

3.4 RESULT

A synthetic population size of 58,354,744 was created to represent the Thai population; 2.55% were <2 years, 6.36% were 2-5 years, 22.43% were 6-18 years, 62.54% were 19-65 years, and 6.11% were ≥ 65 years old. There were 4,926,876 people with CMC (8.44%) and 55,550 HCWs (0.1% of adults).

No vaccination scenario

At baseline, incidence of infection gradually increases and peaks on day 127 after the initiation of the first 100 infected agents. At the end of day 180, there are 7,109,427 cumulative new

infected agents. The overall attack rate is estimated to be 12.18%. Of all infection, 4,730,594 infected agents are symptomatic case. Symptomatic attack rate is 8.11%. About 36% of cases occurs in those ≤ 18 years, 59% in 19–64 year olds, and 5% in those ≥65 years old. The highest attack rate occurs in school-age children and adolescent (15.32%) and healthcare workers (76.67%). There are 2,219 influenza deaths.

The overall mortality rate is 3.8 per 100,000 population. The highest death rate occurs in elderly (11.54 per 100,000 population), and healthcare workers (27.52 per 100,000 population). Overall case fatality rate (CFR) is 0.03%, and the highest is found among elderly (0.12%), and people with CMC (0.12%). Specific morbidity and mortality rates are listed in Table 8.

Impact of 100% vaccine coverage for different strategies

Vaccination can reduce influenza incidence and defers the peak of outbreak; the more extended policy, the higher benefit (Figure 11). On day 180 after the initiation of the 100 agents with an infection; vaccination among target population and extended policies has cumulative attack rate range from 0.08% to 6.45%, mortality rate ranges from 0.02 to 1.54 per 100,100 population, depending on the vaccine policy chosen (Table 9). The extended policy to cover children age 2-18 years old provides as much benefit close to 100% vaccine coverage in the total population.

Vaccinating children can reduces influenza morbidity and mortality for both children and adults. In sub-population, for 100% target population policy, the proportions of total cases that can be avoided range from 3.75% to 84.17%. The highest reduction is observed among people with CMC, follow by elderly. The benefit is very small for HCWs (3.75%), compared with other groups that also had influenza vaccine. Those who did not get vaccination has burden reduction almost half. We observe higher vaccine impact with similar pattern when the policy extend to cover children aged 2 to 5 years old. The most extended policy to include children aged 2 to 18

years old can avoid >99% of cases except HCWs (about 77%), adults are prevented even they were not vaccinated (Table 10).

One hundred percent target population policy can prevent death 29.91% to 85.39%. Similar to case reduction; the highest reduction is observed among people with CMC, and lowest among HCWs. Impact of vaccine to prevent death among HCWs is not as high as other groups in all vaccine policies (Table 11).

Impact of vaccine coverage

We show in Figures 12 and 13 the proportion of cases and deaths reduction caused by various vaccine coverage versus no vaccination. The decrement of vaccine coverage from 100% to 75% and 50% coverage has much impact on both target population and target population plus children 2-5 years old vaccine policy. About 40% of the prevented burden are removed if vaccine coverage drops from 100% to 50%. Vaccine coverage has less impact on target population plus children 2-18 years old vaccine policy. The proportion of prevention is still above 90% for both case and deaths even with 50% coverage. We observe similar pattern of decreasing prevention in all sub-population except HCWs, which has low benefit with low vaccine coverage for all vaccine policies.

3.5 DISCUSSION

Our study results are similar to other modeling studies of optimizing influenza vaccine allocation. These studies had consistent results that prioritization of children age 5-19 years old leads to the greatest reduction of the influenza incidence.[74,132-135] However, in term of cost effectiveness, the benefit is greatest for strategy that prioritize to population with a high risk of

complications. This depend on age-structure, if a country has a high proportion of elderly, it would be most cost effective to vaccinate elderly people.[74,135]

Children play a primary role in influenza transmission because they have a tendency to acquire and shed influenza. Our study is in agreement with those of influenza's spread, where school-aged children and youths were identified as the age group most likely to transmit influenza because of the nature of their contact networks.[136-138] We also found that preschool age children are an important role of the transmission, similar to study of identifying pediatric age groups for influenza vaccination.[139] There may be benefit in vaccinating children older than the current targeted age of 6 months through 2 years of age. Vaccinating preschool and school-aged children yields a substantial reduction of influenza morbidity and mortality. Vaccinating children produces both direct prevention in the children vaccinated and indirect prevention in the rest of the population as a result of herd protection.[73,140,141] The obvious benefit is observed from vaccine scenario that include school-aged children because this age group has the highest attack rate and would be the source of secondary infections to other household members. The vaccine's impact is still impressive even the vaccine coverage drops to 50%. This is a more practical strategy because it is less likely that a vaccine policy can achieve 100% coverage. Also, a school-based vaccination program is a feasible strategy that can enhance the current influenza vaccination program administered at the healthcare settings.

The results of our simulation model demonstrate that the current Thailand influenza vaccine has moderate effect to reduce influenza morbidity (about 47%), with a little higher reduction of mortality (about 60%). This is because the policy targets those who are likely to have severe complications if they got influenza (such as infant, elderly and people with medical condition), rather than those people who are likely to transmit the disease (such as school-aged

children). With this level of burden reduction, this policy seems to be not effective enough to prevent influenza in Thailand. In 2014, the Thailand Ministry of Public Health prepared influenza vaccines for current vaccine policy approximately 3,400,000 doses, which cover about 60% of target population. This may not achieve 47% morbidity and 60% mortality reduction as we assumed 100% vaccine coverage in our simulation. To reach 100% coverage, Thailand has to prepare about 6,000,000 doses of vaccine, but this cost may limit the policy.

Base on Thailand's population registration in year 2013, children aged 2-5 years old are 4.8% of total population. If the vaccine policy extend to cover these children (assumed 100% coverage), Thailand has to prepare an additional 78% of vaccine (about total 10.5 million doses), and can avoid influenza cases and deaths 73% and 79% respectively. However, it is difficult to reach that such high vaccine coverage. Then, the mitigation of influenza burden would decrease. Considered school-aged children, they are 17.4% of total population. If the policy extend to cover this age group (assumed 100% coverage), Thailand has to prepared additional 168% of vaccine (about total 15.7 million doses), and can avoid influenza cases and deaths >99%. Alternatively, if this policy aims at 50% coverage of all target population, this will requires 7.8 million doses of vaccine, but still can avoid about 93% of cases and 94% of deaths.

Vaccinating healthcare workers seems to be not effective intervention. This is because we assumed 88% of sick people visit healthcare settings,[126] that means hospitals will pool with many influenza cases. When patients visit healthcare facilities, they will interact closely with HCWs. Assuming vaccine efficacy at 73%, even 100% vaccine coverage among HCWs will has little benefit when they have high number of effective contact to infected individuals. Efficacy of influenza vaccine is not quite high because antigenic drift of influenza viruses allows the seasonal viruses to escape the neutralizing activity of antibodies induced by previous infections

or vaccination.[142] This is confirmed by vaccine policy that includes all children and youths, it lower the incidence amongst HCWs significantly. Healthcare workforce is very crucial in medical care. If HCWs are infected, they will not be able to perform their services and could infect other patients and colleagues. Cross-transmission of influenza infection from healthcare workers to patients has been described.[33-36] To prevent outbreak in healthcare settings, we should not rely on only vaccine strategy, we need to consider additional intervention such as personal protection and hygiene.

This study has some strengths. We conducted a national-scale study which clinical trials and epidemiological studies may be difficult to perform. Including people with CMC and pregnant women makes more complete picture of influenza burden and allow us to evaluate impact of vaccine on all target populations in the vaccine policy. Our study has some limitations. All computer models are simplification of reality and cannot account for every possible factor or interaction. We considered all HCWs as a uniform group. In fact, they may have different chance of contacting patients based on their duties. Our model only included HCWs in secondary and tertiary care hospitals and did not include sub-district health promoting hospitals (primary care centers) in the country. Because of the computational costs involved, the current results do not include a sensitivity analysis that involved the underlying transmission parameters and case fatality parameters.

In conclusion, current Thailand's vaccine policy and coverage may not effective enough to control influenza. Extended policy to vaccinate preschool and school-aged children is optimizing strategy. Vaccination alone may not prevent influenza outbreak in healthcare settings. Modeling is a tool to provide decision makers with information for influenza preparedness and control.

Acknowledgments

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3.6 TABLES

Table 8 Specific morbidity and mortality rate of influenza in no vaccination scenario

Population	Number	Case		Death	
		Number	Attack rate (%)	Number	Death rate (per 100,000)
All	58,354,744	7,109,427	12.18	22,219	3.80
Age (years)					
<2	1,489,947	161,669	10.85	47	3.15
2-5	3,709,878	422,586	11.39	80	2.14
6-18	13,091,312	2,005,482	15.32	382	2.92
19-65	36,495,519	4,179,841	11.45	1,299	3.56
≥65	3,568,088	339,850	9.52	412	11.54
People with CMC	4,926,876	544,238	11.05	659	13.38
Pregnant women	720,069	86,850	12.06	27	3.67
Healthcare workers	55,550	42,590	76.67	16	27.52

Table 9 Morbidity and mortality rate of influenza by different vaccine policy

Vaccine policy	Case		Death	
	Number	Attack rate (%)	Number	Death rate (per 100,000)
No vaccination	7,109,427	12.18	22,219	3.80
100% of total population	63	<0.01	0	0.00
100% of target population*	3,763,862	6.45	897	1.54
100% of target population* + children age 2-5 yrs old	1,948,694	3.34	460	0.79
100% of target population* + children age 2-18 yrs old	44,504	0.08	100	0.02

* Target population: healthcare personnel, persons who have chronic health conditions, all persons aged ≥ 65 years, all children from 6 months through 2 years of age, pregnant women

Table 10 Proportion of cases prevented, by different vaccine policy (100% coverage)

Population	% of cased that can be avoided† (95%CI)		
	Target population*	Target population* plus children 2-5 years old	Target population* plus children 2-18 years old
Total population	47.06% (46.97, 47.15)	72.59% (72.51, 72.67)	99.37% (99.30, 99.44)
Age (years)			
<2	62.62% (62.08, 63.17)	84.11% (83.61, 84.61)	99.65% (99.19, 100.11)
2-5	45.12% (44.76, 45.48)	89.90% (89.60, 90.20)	99.76% (99.48, 100.05)
6-18	41.86% (41.70, 42.02)	68.99% (68.85, 69.14)	99.78% (99.65, 99.91)
19-65	46.57% (46.46, 46.68)	70.81% (70.71, 70.91)	99.10% (99.01, 99.19)
≥65	78.74% (78.38, 79.09)	88.70% (88.36, 89.04)	99.71% (99.39, 100.03)
People with CMC	84.17% (83.90, 84.44)	91.60% (91.34, 91.86)	99.78% (99.53, 100.03)
Pregnant women	66.35% (65.62, 67.08)	81.24% (80.55, 81.92)	99.50% (98.88, 100.13)
Healthcare workers	3.75% (3.09, 4.41)	7.28% (6.60, 7.95)	76.60% (75.98, 77.22)

* Target population: healthcare personnel, persons who have chronic health conditions, all persons aged ≥ 65 years, all children from 6 months through 2 years of age, pregnant women

† % of cases that can be avoided = (attack rate of no vaccination - attack rate of vaccine policies) x 100 ÷ attack rate of no vaccination

Table 11 Proportion of deaths prevented, by different vaccine policy (100% coverage)

Population	% of death that can be avoided† (95%CI)		
	Target population	Target population + children 2-5 years old	Target population + children 2-18 years old
Total population	59.61% (54.68, 64.54)	79.27% (74.70, 83.85)	99.47% (95.29, 103.64)
Age (years)			
<2	57.14% (22.97, 91.31)	82.07% (51.02, 113.11)	99.39% (70.72, 128.07)
2-5	44.86% (17.45, 72.28)	89.73% (66.62, 112.84)	99.82% (77.79, 121.85)
6-18	43.85% (31.31, 56.38)	71.90% (60.55, 83.26)	99.85% (89.81, 109.89)
19-65	57.93% (51.44, 64.41)	77.02% (70.99, 83.05)	99.26% (93.80, 104.72)
≥65	82.66% (72.20, 93.12)	90.88% (80.79, 100.97)	99.69% (90.02, 109.36)
People with CMC	85.39% (77.22, 93.56)	92.22% (84.29, 100.14)	99.67% (92.03, 107.32)
Pregnant women	72.97% (30.00, 115.94)	87.57% (47.14, 127.99)	98.92% (60.59, 137.25)
Healthcare workers	29.91% (-35.47, 95.28)	28.97% (-36.58, 94.53)	82.24% (27.85, 136.64)

* Target population: healthcare personnel, persons who have chronic health conditions, all persons aged ≥ 65 years, all children from 6 months through 2 years of age, pregnant women

† % of deaths that can be avoided = (mortality rate of no vaccination - mortality rate of vaccine policies) x 100 ÷ mortality rate of no vaccination

3.7 FIGURES

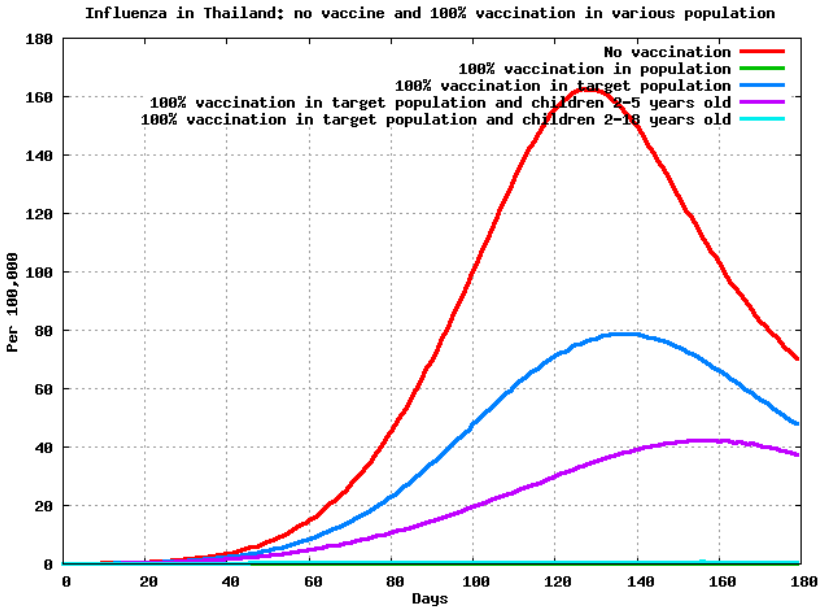

Figure 11 Daily incidence of influenza infection for different vaccine policies

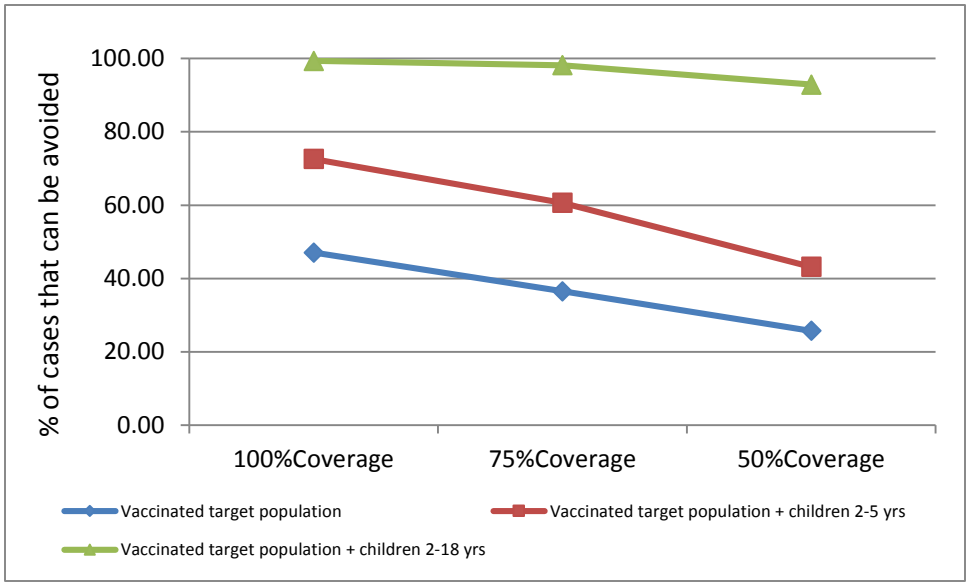

Figure 12 Proportion of cases that can be avoided for three vaccine coverage

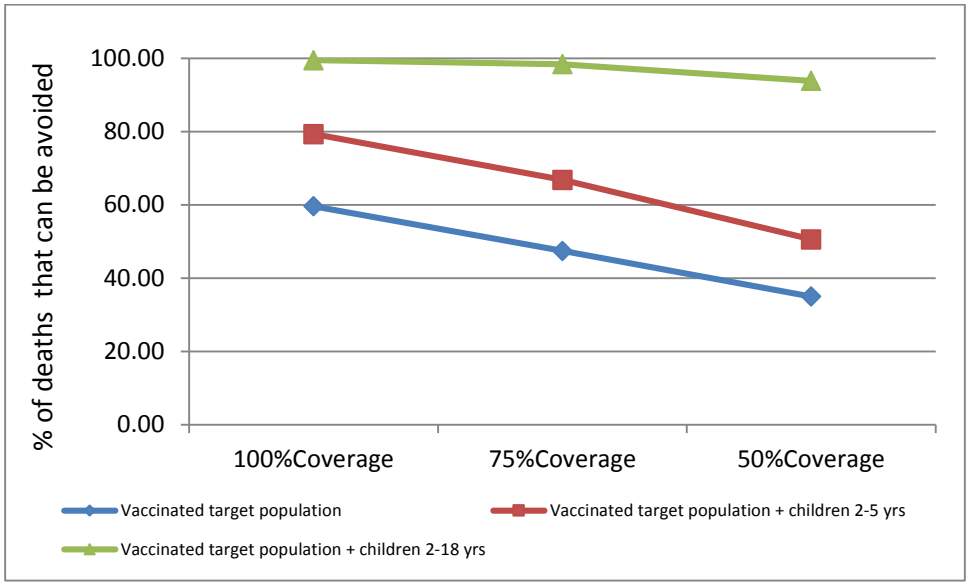

Figure 13 Proportion of deaths that can be avoided for three vaccine coverage

4.0 MANUSCRIPT 3: EFFECT OF PROMPT NON-PHARMACEUTICAL INTERVENTIONS ON INFLUENZA OUTBREAK

Manuscript in preparation

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4.1 ABSTRACT

Some non-pharmaceutical interventions such as mask wearing or hand washing have been shown protective effect in reducing influenza illness. They are inexpensive and can be implemented widely even in limited healthcare resource settings. However, there was a few study that model their impact on influenza burden on population. The projection of influenza burden was studied by fitting an agent-based computer simulation model. The model contains a 58,354,744 synthetic Thai population, incorporates people with CMC and HCWs. At start, 100 agents were randomly assigned for initial infection. The model simulated the interactions of individuals with others at household, school, workplace, and hospitals over 180 days. Impacts of face mask wearing and hand washing on morbidity and mortality were simulated at 10%, 25%, 50%, 75% and 100% coverage. 100% compliance of combined policy can avoid morbidity and mortality >99% in total population. The benefit is slightly small for HCWs (97.19% case reduction). If the population can afford >50% compliance of the intervention, the proportion of cases reduction still >98% for all adherence of mask wearing. Face masks and hand washing are effective strategies for countries with limited supplies of vaccines and antiviral drugs. Modeling is a tool to provide decision makers with information for influenza preparedness and control.

Key words: Influenza, Mask, Hand washing, Thailand, Computer simulation

4.2 INTRODUCTION

Influenza vaccination and antiviral drugs have been effective interventions against seasonal influenza outbreaks in developed countries.[123-125] In order for vaccines to provide protection against infections, the vaccine strain must be antigenically similar to the epidemic or pandemic strain. Consequently, vaccine production cannot begin until the circulated viral strain has been isolated and the lead time for vaccine production is typically 4–6 months or more. So, vaccination is not a prompt intervention if an outbreak of new viral strains occur. Antiviral drug might be effective to reduce influenza burden,[6,8] but its stockpiling is very expensive and might not be practical to many countries. As a result antiviral prophylaxis is not a standard policy in developing countries including Thailand. Instead, non-pharmaceutical interventions are more common; such as social distancing, isolation and quarantine, personal protection and hygiene measures (hand washing and face mask wearing).

In the event of an influenza pandemic, effective vaccine and antiviral drugs may be lacking. Disrupting environmental transmission of the influenza virus using non-pharmacological interventions will be the only viable strategy to protect the public.[143] However, delayed implementation of these interventions might provide less benefit.[144,145]

Various non-pharmaceutical intervention strategies are a first line of defense against outbreak of infectious diseases because they can be implemented rapidly,[146] and not depend on influenza viral strains like vaccination. Many studies model effect of social distancing such as school closure and travel restriction. School closure has been considered a useful strategy to control the spread of influenza; however, its effect was not consensus. Some of these studies demonstrated school closure are capable of mitigating influenza overall attack rate.[145,147,148] Several studies demonstrated small or no reduction in the overall attack rate but can delay the

peak of epidemic.[149-152] These studies showed that to gain benefit either attack rate reduction or delay the epidemic, duration of closing school should be maintained relatively long (about 4-8 weeks). This makes school closure policy a significant economic impact and community controversial as parent have to leave form work to care for unattended-school children.[98,99]

Some non-pharmaceutical interventions such as mask wearing or hand washing have been shown protective effect in reducing influenza illness and upper-respiratory tract infections from many controlled trials.[104,106-114] Adherent use of surgical masks significantly reduces the risk for influenza-like illness (ILI) infection among household members of ILI patients, with a hazard ratio equal to 0.26.[104] Hand washing program can reduce respiratory illness 21%-52%.[106-112] In contrast, some studied showed no protective effect of face mask use alone or hand washing alone on ILI or influenza, but revealed effectiveness of both interventions combined. The combined intervention can reduce respiratory illness range from 35%-51%.[113,114] Face masks are used to limit influenza transmission by minimizing the distribution of large secretion droplets produced during sneezing or coughing. Hand washing can reduce the transmission by indirect contact with contaminated common surfaces. They are non-invasive interventions and do not depend on healthcare personnel. Both interventions are inexpensive and can be implemented widely even in limited healthcare resource settings.

Face masks have been stockpiled for influenza preparedness and are currently recommended to prevent influenza infection in several countries, including Thailand. The effective management and control of infectious disease is increasingly done with substantial input from mathematical models and simulations, which are used to provide predictions about the likely success of public health measures.[47] Therefore, it is becoming increasingly important that epidemiological models produce accurate quantitative prediction of disease and impact of

control measures. There are a few study which use computer simulation model the impact of face masks on influenza burden on population. These studied reported that face mask use is an effective intervention strategy in delaying and influenza pandemic and reducing the spread of influenza.[153-155] However, there is no published study that simulate impact of hand washing alone or combined face mask wearing and hand washing at population level. In practice, it is less likely that a public health campaign will suggest a single intervention, neither face mask use nor hand washing. Instead, both intervention often be recommended together.

The role of prompt non-pharmaceutical interventions on influenza outbreak control is not well understood in Thailand. The modeling of face mask use and hand washing interventions can be used as evidence for introduction for new intervention policies. This study has aim to identify effect of promoting health behavior interventions (hand washing and face mask wearing) on influenza outbreak control.

4.3 METHODS

Synthetic population data

A synthetic population (with school and workplace assignments) of Thailand was developed by the Research Triangle Institute (RTI International).[83] In summary, RTI International used a proportional iterative method[82] to generate an agent population from census aggregated data. Thai census data (year 2000) on household size and age distributions were used to generate the synthesized agents and households. Each agent had a set of socio-demographic characteristics and that included age, sex, employment status, occupation, and household. School data (year 2011) from the Thai Ministry of Education[84] on ≈38,000 schools were used to determine the

distribution of school sizes, number and proportions of children in school as a function of age for school assignment. The schools assignment method was based on the assumption that students are enrolled at the closest school having adequate capacity. Data of Thailand Industrial census in year 2007[85] were used for workplace assignment. The data indicated numbers and percentages of workers by size of work place (1 - 15, 16 - 25, 26 - 30, 31 - 50, 51 - 200, and >200 workers). The locations of workplaces were generated. Then, each non-school age population was assigned to a workplace such that the distribution and capacity of each workplace was appropriate.

We used data of the actual hospitals in Thailand[86] to create synthetic hospitals with estimated number of HCWs. The method assumed that the number of HCWs who interact with patients was proportional to the number of beds by the value of 1 to 1 (e.g. a hospital with 100 beds would have 100 HCWs who interact with patients). The simulation then found a synthetic workplace with approximately the same number of employees and moved the assigned employees to work in the hospital as healthcare workers (HCWs). To determine which hospital a family will visit, we used a gravity model where the probability of going to a given hospital was determined by the (number of beds) / (distance from household to hospital)^2.

We randomly assigned synthetic population to had chronic medical condition (CMC) based on the 4th National Health Examination Survey of Thailand (year 2008 - 2009). The survey reported that among people age > 15 years old, prevalence of asthma was 3%, chronic obstructive pulmonary disease (COPD) was 0.4%, chronic renal disease was 0.8%, diabetes was 6.9%, and coronary heart disease (CHD) was 1.4%. Prevalence of diabetes and CHD was stratified by age group. The point prevalence of pregnant women was estimated from average of age-specific fertility rate year 2002 - 2011. We assumed people with CMC will visit hospital once a month for disease follow-up and getting drugs.

Agents move among their households, assigned workplaces or hospitals (for employed adults), schools (for school-aged children) and various locations in the community, where they interact with other agents who were household members, workplace mate, and classmate.

Disease and model parameterization

Disease parameters and assumptions followed the process described in study by Cooley et al.[80] and systematic review of Zhou et al.[81] Individuals are classified according to theirs infection and immune status as either susceptible (S), latent or exposed (E), infectious (I), or recovered (R). All individuals are initially susceptible to influenza until infectious individuals are introduced into the model. Each newly infected individual entered a latent state. During this time, the agent was infected but not yet infectious to others. We assumed that infectiousness and symptoms began at the same time as the viruses are shed via droplets produced when infected people cough or sneeze. Thus latent period (the time from infection to when a host is able to transmit the pathogen) was approximate to incubation period. Then, the agent moves to the infectious state, in which the agent may infect others. Two-third of infected agents develop symptoms.[64,76,117] Finally, the agent enters the recovered state and remains immune to subsequent infections.

We assumed the following base probability values for hospitalization, outpatient-care and case fatality: outpatient-care probability = 0.88,[126] hospitalization probability = 0.22 (from database of Thailand Notifiable Disease Report, that was a proportion of inpatient among reported influenza cases), case fatality probability = 0.0000715.[127] Risk factors for severe outcomes following pandemic influenza A (H1N1) infection are similar to those for seasonal influenza.[128] We applied risk ratios of hospitalization or death from Van Kerkhove et al.[128] to those influenza cases who had chronic medical condition(s) or pregnancy in our simulations. We

assumed that if an agent is hospitalized, then others in their household may visit them with a probability of 0.25 on each day that they remain hospitalized.

The projection of influenza burden was studied by fitting an agent-based computer simulation model (ABM). This study used a Framework for Reconstructing Epidemiological Dynamics (FRED) for modeling. FRED is an open source, modeling system developed by the University of Pittsburgh Public Health Dynamics Laboratory in collaboration with the Pittsburgh Supercomputing Center (PSU) and the School of Computer Science at Carnegie Mellon University.[79] The model was a stochastic, spatially structured, individual-based discrete time simulation. Agents are co-located in households, with households being constructed to reflect typical generational structure while matching empirical distributions of age structure and household size for Thailand.

The probability that an infected agent transmitted influenza to susceptible agent depended on the rate of potentially infectious contacts, and the probability per contact of transmitting influenza. Every susceptible agent who contacted an infectious agents had a probability of disease transmission (per contact), derived from prior studies of the 1957–1958 Asian influenza pandemic.[7,64,76] As in Cooley et al.[80], we assumed that 50% of sick agents stay at home and do not interact with any agents outside of the household. Additionally, we assumed that all community contacts increase by 50% on weekends. The model was calibrated using the Ferguson et al. approach from historical (1957–1958, 1968–1969) influenza pandemics.[7]

We specifically used the 30-70 rule developed in which 30% of all transmission occurred in the household and 70% occurred outside the household (33% in the general community, and 37% in schools and workplaces)[7]. The strategy was to estimate mean contact rate per day at each location that produced and epidemic that satisfied the 30-70 rule calibration criteria. To achieve

this rule, within household contacts were treated differently than other locations. We assumed that each pair of agents within a household make contact each day with a specified probability. This probability is tuned as part of the calibration step to achieve the 30-70 target distribution. At the start of each simulation, 100 agents were randomly assigned for initial infection. The individuals interact daily with others in the same household, school and workplace with a fixed mean number of people that they contact per day (from calibration step). We considered influenza R_0 = 1.4. The simulations were run over 180 days. Each presented result is the average of 7 simulation runs for one experiment (one intervention strategy).

Efficacy and strategies of face mask use plus hand washing

When infected agents had symptom of influenza, they had to wear a standard surgical mask and changed daily. We assumed that they wore face mask at all time according to their adherence. The adherence was assumed for 3 durations; only the first day of symptom, first 2 days of symptoms, and entire period of symptoms. Hand washing was defined as washing hands using soap and water for ≈45 seconds before and after meals, after using the bathroom, and after coughing or sneezing on hands. We modeled the combined intervention and used an efficacy value of 0.33 derived from the Cowling et al.'s study.[114] This means the combined intervention can reduce influenza infection by 33%.

In reality, compliance to a control measure may be less than 100%, especially for the health behavior, a series of compliance levels (10%, 25%, 50%, 75% and 100%) were simulated for both face mask use and hand washing.

Computational specifics

Simulations were performed on Blacklight at PSU. Blacklight is an SGI servers, clusters and supercomputers, shared-memory system comprising 256 blades. Each blade holds 2 Intel Xeon X7560 (Nehalem) eight-core processors, for a total of 4096 cores across the whole machine. Each core has a clock rate of 2.27 GHz. Each experiment (7 simulation runs in parallel) is run using parallel computing over 16 computer nodes, taking an average of 8 hours on each experiment (128 hours of total computer time).

4.4 RESULTS

A synthetic population size of 58,354,744 was created to represent the Thai population; 2.55% were <2 years, 6.36% were 2-5 years, 22.43% were 6-18 years, 62.54% were 19-65 years, and 6.11% were $\geq$ 65 years old. There were 4,926,876 people with CMC (8.44%) and 55,550 HCWs (0.1% of adults).

No intervention scenario

At baseline, incidence of infection gradually increases and peaks on day 127 after the initiation of the first 100 infected agents. At the end of day 180, there are 7,109,427 cumulative new infected agents. The overall attack rate is estimated to be 12.18%. Of all infection, 4,730,594 infected agents are symptomatic case. Symptomatic attack rate is 8.11%. About 36% of cases occurs in those $\leq$ 18 years, 59% in 19–64 year olds, and 5% in those $\geq$65 years old. The highest attack rate occurs in school-age children and adolescent (15.32%) and HCWs (76.67%). There are 2,219 influenza deaths. The overall mortality rate is 3.8 per 100,000 population. The highest death rate occurs in elderly (11.54 per 100,000 population), and healthcare workers (27.52 per

100,000 population). Overall case fatality rate (CFR) is 0.03%, and the highest is found among elderly (0.12%), and people with CMC (0.12%). Specific morbidity and mortality rates are listed in Table 12.

Impact of combined face mask and hand washing, 100% coverage

On day 180 after the initiation of the hundred agents with an infection; combined face mask wearing and hand washing policies has number of cases range from 1,811 to 4,090 cases (cumulative attack rate <0.01%), number of deaths range from 1 to 2 deaths (mortality rate <0.01 per 100,100 population), depending on the adherence of face mask wearing (Table 13).

In sub-population, for 100% compliance of combined policy with 1 day wearing mask, the proportions of total cases that can be avoided are >99.9% except among HCWs that is 97.19%. This is because majority of cases is observed among HCWs (29.3%). If compliance of wearing mask increase, we observe similar pattern of increasing prevention in all sub-population. Wearing mask for whole period of symptom can avoid case among HCWs up to 98.62%.

In case the population cannot achieve 100% coverage of the combined intervention, the protective effect decline, especially when the coverage drops to 10% (Table 14). However, if the population can achieve >50% compliance of the interventions, the proportion of cases reduction still >98%.

4.5 DISCUSSION

Our results suggest that face mask use among symptomatic influenza cases combined with hand washing at population level can decrease transmission significantly to contain the outbreak. Even its efficacy is much smaller than influenza vaccine, but these interventions can be applied to

broader population and provides similar benefit to the population. These hygiene interventions are intended to reduce the density of virus and infectiousness along routes of transmission sources, thus reducing virus exposure and infection risk within the population. Our findings are in agreement with study of Brienen et al.[154] and Tracht et al.[155], that face mask use is effective strategy to mitigate influenza transmission. There are some differences in detail of intervention; combined face mask use and hand washing versus only face mask use, face mask use among symptomatic individuals versus the use in general population-both healthy and infected people). However, using mask only in infected individuals is still effective.[155]

Impact of hygiene interventions are usually depend on the compliance in the population. We often found that willingness to use these intervention is low unless there are some threat; for example, the 2003 Severe Acute Respiratory Syndrome (SARS) epidemic. In Hong Kong, the residents reported high proportion of using masks and washing their hands after contact with potentially contaminated objects during the SARS outbreak.[103,156,157] Similarly, during influenza outbreak, people might have greater concern. So, outbreak investigation and control team can encourage people to have higher compliance to hygiene interventions. We observed that even compliance of the intervention is low, the impact of intervention is still high, similar to study of Tracht et al.[155] However, their study reported smaller case reduction, with compliance 10%-50%, the face mask intervention can reduce attack rate 5.2%-8.1% (compare with 40.9%-98.0% in our study). This may due to a very low effectiveness they used in their models (0.05).

The adherence of face mask use does not significantly affect proportion of case reduction unless the compliance of mask wearing is $\leq$25%. This might be because viral shedding peak on day 2 after infection (about first day of symptom).[117] This can be inferred that wearing mask at

least first 2 days of symptoms is recommended, but wearing for the whole period of symptom would be the best.

Impact of intervention among HCWs is slightly lower than other groups. This is because we assumed 88% of sick people visit healthcare settings,[126] that means hospitals will pool with many influenza cases. When patients visit healthcare facilities, they will interact closely with HCWs and cause HCWs have repeated exposures. Cross-transmission of influenza infection from healthcare workers to patients has been described.[33-36] To prevent outbreak in healthcare settings, we may consider vaccine intervention combined with personal protection and hygiene.

We caution to not overinterpret the modeling results. Assuming 88% of sick people visit healthcare settings and about 20% of them are hospitalized, this added some level of isolation in a background. So, interventions are in addition to standard physician visits and hospitalization. Isolation and quarantine are also effective intervention. Halloran et al. simulated the effectiveness of a set of intervention strategies; combinations called targeted layered containment (TLC) of influenza antiviral treatment and prophylaxis and non-pharmaceutical interventions of quarantine, isolation, school closure, and social distancing. They suggested that timely implementation of the TLC could substantially lower the influenza attack rate.[76] The results in this study need to be viewed more as helping to influenza outbreak preparedness, rather than being predictive of the precise effectiveness of the interventions.

Our study has some limitations. All computer models are simplification of reality and cannot account for every possible factor or interaction. We considered all HCWs as a uniform group. In fact, they may have different chance of contacting patients based on their duties. Our model simply use a same compliance for both face mask wearing and hand washing. Because of

the computational costs involved, the current results do not include a sensitivity analysis that involved the underlying transmission parameters and case fatality parameters.

In conclusion, face masks and hand washing are effective strategies (in addition to case isolation) for countries with limited supplies of vaccines and antiviral drugs. Modeling is a tool to provide decision makers with information for influenza preparedness and control.

Acknowledgments

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4.6 TABLES

Table 12 Specific morbidity and mortality rate of influenza in no intervention scenario

Population	Number	Case		Death	
		Number	Attack rate (%)	Number	Death rate (per 100,000)
All	58,354,744	7,109,427	12.18	22,219	3.80
Age (years)					
<2	1,489,947	161,669	10.85	47	3.15
2-5	3,709,878	422,586	11.39	80	2.14
6-18	13,091,312	2,005,482	15.32	382	2.92
19-65	36,495,519	4,179,841	11.45	1,299	3.56
≥65	3,568,088	339,850	9.52	412	11.54
People with CMC	4,926,876	544,238	11.05	659	13.38
Pregnant women	720,069	86,850	12.06	27	3.67
Healthcare workers	55,550	42,590	76.67	16	27.52

Table 13 Morbidity and mortality rate of influenza in combined fask mask and hand washing policy by different adherence of face mask wearing

Vaccine policy	Case		Death	
	Number	Attack rate (%)	Number	Death rate (per 100,000)
No Intervention	7,109,427	12.18	22,219	3.80
100% of combined intervention (1 day wearing mask)	4,090	0.01	2	<0.01
100% of combined intervention (2 days wearing mask)	2,199	<0.01	1	<0.01
100% of combined intervention (wearing mask for whole period of symptom)	1,811	<0.01	1	<0.01

Table 14 Morbidity rate of influenza in combined fask mask and hand washing policy by coverage and adherence

Coverage	1 day wearing mask		2 day wearing mask		Wearing mask for whole period of symptom	
	Number of case	Attack rate (%)	Number of case	Attack rate (%)	Number of case	Attack rate (%)
100%	4,090	0.01	2,199	<0.01	1,811	<0.01
75%	22,601	0.04	18,197	0.03	7,972	0.01
50%	140,124	0.24	106,313	0.18	66,745	0.11
25%	1,224,912	2.10	1,067,708	1.83	755,206	1.29
10%	4,202,914	7.20	3,950,843	6.77	3,577,559	6.13

5.0 CONCLUSIONS

Modeling is a tool to provide decision makers with information for influenza preparedness and control. This dissertation used a large-scale agent-based framework of infectious diseases, namely FRED, to simulate agent-based models to estimated influenza burden in Thailand and assess impact of vaccine allocation policy and non-pharmaceutical interventions (mask wearing and hand washing). A new Thai synthetic population was created for this study, and is available for researchers who interest to model infectious disease in Thailand (Contact: Dr.Yongjua Laosiritaworn (yongjua@gmail.com), Dr. John Grefenstette (gref@pitt.edu), or the University of Pittsburgh Public Health Dynamics Laboratory (https://www.phdl.pitt.edu/)). This dissertation estimated influenza burden in Thailand and assessed impact of vaccine allocation policy and non-pharmaceutical interventions (mask wearing and hand washing).

Many modeling studies estimated influenza R_0 using epidemiologic data from previous influenza pandemic or seasonal influenza in developed countries. Despite Thailand had different social contacts and lifestyles compare to developed countries, this dissertation found that Thailand influenza R_0 is comparable to the range of those estimated seasonal influenza R_0 from those countries. This finding is in agreement to use R_0 value 1.4 - 1.5 to model influenza in Thailand. Modeling results of no-intervention scenario found that influenza incidence from simulation was markedly higher than reported case in the National Notifiable Disease Report. This represented a tip of iceberg phenomenon of case-based surveillance.

Influenza vaccination has been an effective intervention against influenza illness. This dissertation modeled impact of various vaccine strategies to find optimal vaccine policy for Thailand. The simulation results demonstrated that the current Thailand influenza vaccine policy (year 2014) can reduce influenza morbidity and mortality about 47% and 60% respectively (assumed 100% coverage). However, availability of vaccine in 2014 (approximately 3,400,000 doses) cover about 60% of target population and may reduce the benefit of burden reduction. To reach 100% coverage, Thailand has to prepare about 6,000,000 doses of vaccine, but this cost may limit the policy. Extended policy to vaccinate preschool and school-aged children yields a substantial reduction of influenza morbidity and mortality and is an optimal vaccine strategy. Even 50% coverage of this extended policy can avoid about 93% of cases and 94% of deaths, but will requires 7,800,000 doses of vaccine. In case of many influenza patients visit hospitals, single intervention of vaccinating HCWs seems not effective enough to prevent outbreak in healthcare settings. This is because influenza vaccine efficacy is not quite high and cannot provide effective prevention if there are high number of contact between infected individuals and HCWs. To prevent outbreak in healthcare settings, intervention such as personal protection and hygiene should be considered add on vaccine strategy.

In the event of an influenza pandemic, effective vaccine and antiviral drugs may be lacking. Various non-pharmaceutical intervention strategies are a first line of defense against the outbreak. This dissertation modeled impact of face mask use plus hand washing intervention on outbreak control. The simulation based on scenario that 88% of symptomatic influenza cases will visit hospitals and about 22% of them have probability to be hospitalized, this results in some level of case isolation in healthcare settings. The results suggested that face mask use among symptomatic influenza cases combined with hand washing at population level can decrease

transmission significantly to contain the outbreak. Wearing mask at least first 2 days of symptoms is recommended, but wearing for the whole period of symptom would be the best. Face masks plus hand washing (and case isolation) are effective strategies for countries with limited supplies of vaccines and antiviral drugs.

This study has some strengths. Investigators conducted a national-scale study which clinical trials and epidemiological studies may be difficult to perform. Including people with CMC and pregnant women makes more complete picture of influenza burden and allow us to evaluate impact of vaccine on all target populations in the vaccine policy. The study has some limitations. All computer models are simplification of reality and cannot account for every possible factor or interaction. Because of the computational costs involved, the current results do not include a sensitivity analysis that involved the underlying transmission parameters and case fatality

5.1 PUBLIC HEALTH SIGNIFICANCE

Influenza is one of re-emerging infectious disease in Thailand. Influenza modeling provides information of probable true burden of disease and impact of various control measures. These can help in planning of influenza preparedness. This dissertation provided information for health policy makers to guide optimized target population for vaccine, and budget allocation for face mask, and hand sanitizer campaigns. To prevent influenza outbreak in healthcare settings, triage for respiratory diseases and strengthening hygiene and personal protection are recommended. General population should be advised for sick leave/self isolation, and encouraged hygiene and personal protection.

5.2 FUTURE RESEARCH

Future research should concentrate on further modeling the cost-effectiveness of influenza vaccine policy in Thailand, and impact of intervention for influenza (or infectious respiratory diseases) prevention in healthcare settings. Additionally, some assessment should be conducted. These include influenza surveillance evaluation, willingness and compliance of face mask use and hand washing. These will provide additional information to guide policy planners in influenza preparedness in Thailand.

5.3 ACKOWLEDGEMENTS

Support for this work is provided in part by the National Institute of General Medical Sciences under MIDAS grant 1U54GM088491-01 and by the Vaccine Modeling Initiative, funded by the Bill and Melinda Gates Foundation. This work used the Extreme Science and Engineering Discovery Environment (XSEDE), which is supported by National Science Foundation grant number ACI-1053575. The authors thank William D Wheaton and RTI International for creating a Thai synthetic population. We are grateful to David Galloway for adding features to FRED and helping run the simulation on the Blacklight at PSC.

APPENDIX A: SUPPLEMENTARY METHODS

A1: SYNTHETIC POPULATION AND ALLOCATION

1. Generating synthesized households and persons

Thai census data (year 2000) on household size and age distributions were used to generate the synthesized agents and households. The household locations were generated and each household in the database was represented as a geographic information system (GIS) "point feature". Point features are unique x,y locations containing descriptive tabular attributes. Then population records were generated for all households. Each agent had a set of socio-demographic characteristics and daily behaviors that included age, sex, employment status, occupation, and household location and membership.

1.1. Assigning agents to schools

School data (year 2011) from the Thai Ministry of Education on ≈38,000 schools were used to determine the distribution of school sizes, number and proportions of children in school as a function of age for school assignment. The locations (point) of each school were generated from their address code (province, district, and sub-district). The schools assignment method was based on the assumption that students are enrolled at the closest school having adequate capacity. This assumption is necessary because no national data source of school catchment areas exists. The school allocation method assigns agents who are of school age (4 to 18 years of age) to

schools. The spatial allocation is based on a minimum path algorithm such that available students of a certain grade level will be assigned to the closest school that has capacity for students of that grade level. Children who are 4 to 6 years old are assigned only to schools that have kindergarten enrollment. The remaining children, ages 7 to 18, are assigned to appropriate schools; primary school (7 to 12 years old), lower-secondary schools (12 to 15 years old), and higher-secondary schools (15 to 18 years old). Children who enroll in the same school have the same school identifier; therefore, we know explicitly which children may come into contact with each other based on their school assignments.

1.2. Assigning agents to workplaces

Data of Thailand Industrial and Business/service census in year 2011 were used for workplace assignment. The data indicated numbers and percentages of workers by size of work place (1 - 15, 16 - 25, 26 - 30, 31 - 50, 51 - 200, and >200 workers) for Bangkok, Bangkok vicinity, and all regions (central, north, northeastern, and south). The locations (point) of workplaces were generated. Then, each agent (non-school age population) is assigned to a workplace such that the distribution and capacity of each workplace was appropriate. Agents who work in the same workplace have the same workplace identifier; therefore, we know explicitly which workers may come into contact with each other based on their workplace assignments.

2. Generating synthesized hospitals and healthcare workers

To create synthetic Hospitals, we used the actual hospitals (the Latitude and Longitude are true) and number of beds in the hospital. We then assume that the number of HCWs who contact patients in a hospital is proportional to the number of beds by the value of 1 to 1 (e.g. a hospital with 100 beds would have 100 HCWs). The simulation then tries to found a synthetic workplace with approximately the same number of employees and then moved the assigned employees to

work in the hospital. To determine which hospital a family will visit, we used a gravity model where the probability of going to a given hospital was determined by the (number of beds) ÷ (distance from household to hospital)^2. Each household was mapped to a hospital randomly. If anyone in the household needs to be hospitalized or visits a hospital, then this is the hospital that they will visit. To make sure that this was consistent throughout all simulations, we stored the mappings of all households to hospitals after the first run of the FRED simulation to a text file and used that file to for each subsequent run, rather than reassigning the households each time.

3. Assigning agents to have medical conditions

For Chronic Conditions, we used the following age group probabilities:

- Asthma
    a. All ages = 0.03
- COPD
    a. Age 16 and over = 0.004
- Chronic Renal Disease
    a. Ages 16 and over = 0.008
- Diabetes
    a. Ages 15 to 29 = 0.006
    b. Ages 30 to 44 = 0.034
    c. Ages 45 to 59 = 0.101
    d. Ages 60 to 69 = 0.167
    e. Ages 70 to 79 = 0.158
    f. Ages 80 and over = 0.115

- Heart Disease
    a. Ages 15 to 44 = 0.003
    b. Ages 45 to 59 = 0.021
    c. Ages 60 to 69 = 0.028
    d. Ages 70 to 79 = 0.049
    e. Ages 80 and over = 0.058

A2: SEVERE OUTCOMES FOLLOWING INFLUENZA

We assumed the following base values for hospitalization, outpatient-care and case fatality:

- Hospitalization probability = 0.22. Hospitalization probability came from database of Thailand Notifiable Disease Report, that was a proportion of inpatient among reported influenza cases.
- Outpatient-care probability = 0.88.[126]
- Case fatality probability = 0.0000715.[127] The experimental parameters use a case fatality probability of 0.0000715 on each of four days of infection, giving a total probability of about 0.00026 or 26 deaths per 100,000 cases.

We then multiplied these base values by the following assumed values for those with chronic Condition:[128]

1) Asthma
    a. Hospitalization multiplier = 1.8
    b. Case Fatality multiplier = 1.7

2) COPD
    a. Hospitalization multiplier = 3.3
    b. Case Fatality multiplier = 7.8
3) Chronic Renal Disease
    a. Hospitalization multiplier = 4.4
    b. Case Fatality multiplier = 22.7
4) Diabetes
    a. Hospitalization multiplier = 0.9
    b. Case Fatality multiplier = 4.0
5) Heart Disease
    a. Hospitalization multiplier = 2.0
    b. Case Fatality multiplier = 9.2
6) Pregnancy (Not a chronic condition, but has multipliers similar to chronic conditions)
    a. Hospitalization multiplier = 6.8
    b. Case Fatality multiplier = 1.9

Note: For simplicity, the multipliers are applied sequentially for those with multiple conditions (e.g. someone with Asthma and COPD would have a case fatality rate of 0.0000715 x 1.7 x 7.8 = 0.0000948)

APPENDIX B: SUPPLEMENTARY TABLES

B1: SUPPLEMENTARY TABLES FOR METHODS

Table 15 Prevalence of diabetes and CHD by age group

Disease	Age group					
	15-29	30-44	45-59	60-69	70-79	≥80
Diabetes	0.6	3.4	10.1	16.7	15.8	11.5
CHD	0.3	0.3	2.1	2.8	4.9	5.8

Source: The 4th National Health Examination Survey of Thailand (year 2008 - 2009) Report

Table 16 Average age-specific fertility rate (per 1,000 female), year 2002 - 2001

Age of mother (Year)	Average rate
15 - 19	47.62
20 - 24	79.09
25 - 29	79.18
30 - 34	57.56
35 - 39	27.18
40 - 44	6.94
45 - 49	0.6

Source: Bureau of Health Policy and Strategy: Thailand Ministry of Public Health

Table 17 Risk ratios (RR) for severe outcomes following 2009 Influenza A(H1N1) infection

Risk factors	RR of hospitalization	RR of death
Respiratory disease	3.3 (2.0 - 5.8)	7.8 (4.9 - 26.6)
Asthma	1.8 (1.2 - 2.6)	1.7 (1.5 - 2.1)
Diabetes	0.9 (0.5 - 1.7)	4.0 (3.1 - 6.9)
Cardiac disease	2.0 (1.5 - 2.2)	9.2 (5.4 - 10.7)
Renal disease	4.4 (4.2 - 4.5)	22.7 (21.0 - 25.4)
Pregnancy	6.8 (4.5 - 12.3)	1.9 (0.0 - 2.6)

Source: Van Kerkhove et al.[128]

Table 18 Age distribution of the synthetic population

Age (years)	**Number**	**Percentage**
<2	1,489,947	2.55
2-5	3,709,878	6.36
6-18	13,091,312	22.43
19-65	36,495,519	62.54
>=65	3,568,088	6.11
Total	58,354,744	

B2: SUPPLEMENTARY RESULTS FOR MANUSCRIPT 2

Table 19 Proportion of cases prevented for target population vaccine policy , by different vaccine coverage

Population	% of cases that can be avoided† (95%CI)		
	100% Coverage	75% Coverage	50% Coverage
Total population	47.06% (46.97, 47.14)	36.49% (36.40, 36.58)	25.70% (25.61, 25.79)
Age (years)			
<2	62.62% (62.08, 63.17)	50.31% (49.74, 50.88)	36.19% (35.60, 36.79)
2-5	45.12% (44.76, 45.48)	34.96% (34.59, 35.33)	24.44% (24.06, 24.82)
6-18	41.86% (41.70, 42.02)	32.06% (31.90, 32.23)	22.13% (21.96, 22.30)
19-65	46.57% (46.46, 46.68)	35.88% (35.76, 35.99)	25.28% (25.16, 25.40)
≥65	78.74% (78.38, 79.09)	65.41% (65.03, 65.78)	48.62% (48.22, 49.01)
People with CMC	84.17% (83.90, 84.44)	69.74% (69.45, 70.02)	51.57% (51.26, 51.87)
Pregnant women	66.35% (65.62, 67.08)	53.47% (52.71, 54.23)	38.94% (38.14, 39.74)
Healthcare workers	3.75% (3.09, 4.41)	3.57% (2.91, 4.23)	2.56% (1.90, 3.22)

* Target population: healthcare personnel, persons who have chronic health conditions, all persons aged ≥ 65 years, all children from 6 months through 2 years of age, pregnant women

† % of cases that can be avoided = (attack rate of no vaccination - attack rate of vaccine policies) x 100 ÷ attack rate of no vaccination

Table 20 Proportion of deaths prevented for target population vaccine policy , by different vaccine coverage

Population	% of deaths that can be avoided† (95%CI)		
	100% Coverage	75% Coverage	50% Coverage
Total population	59.61% (54.68, 64.54)	47.41% (42.27, 52.55)	34.96% (29.62, 40.31)
Age (years)			
<2	57.14% (22.97, 91.31)	50.15% (15.16, 85.15)	41.03% (4.99, 77.08)
2-5	44.86% (17.45, 72.28)	41.98% (14.31, 69.65)	29.73% (1.01, 58.45)
6-18	43.85% (31.31, 56.38)	30.75% (17.70, 43.80)	25.55% (12.30, 38.80)
19-65	57.93% (51.44, 64.41)	45.96% (39.21, 52.71)	32.55% (25.51, 39.59)
≥65	82.66% (72.20, 93.12)	68.19% (57.11, 79.28)	51.61% (39.85, 63.38)
People with CMC	85.39% (77.22, 93.56)	71.34% (62.68, 80.00)	54.58% (45.38, 63.79)
Pregnant women	72.97% (30.00, 115.94)	60.54% (15.52, 105.56)	47.57% (0.50, 94.64)
Healthcare workers	29.91% (-35.47, 95.28)	27.10% (-38.81, 93.01)	18.69% (-48.80, 86.19)

* Target population: healthcare personnel, persons who have chronic health conditions, all persons aged ≥ 65 years, all children from 6 months through 2 years of age, pregnant women

† % of deaths that can be avoided = (mortality rate of no vaccination - mortality rate of vaccine policies) x 100 ÷ mortality rate of no vaccination

Table 21 Proportion of cases prevented for target population + children 2-5 years old vaccine policy , by different vaccine coverage

Population	% of cases that can be avoided† (95%CI)		
	100% Coverage	75% Coverage	50% Coverage
Total population	72.59% (72.51, 72.67)	60.65% (60.56, 60.73)	43.19% (43.10, 43.27)
Age (years)			
<2	84.11% (83.61, 84.61)	74.26% (73.74, 74.78)	57.80% (57.25, 58.36)
2-5	89.90% (89.60, 90.20)	79.48% (79.17, 79.79)	61.60% (61.26, 61.93)
6-18	68.99% (68.85%, 69.14)	57.08% (56.92, 57.23)	40.19% (40.02, 40.35)
19-65	70.81% (70.71, 70.91)	58.50% (58.39, 58.61)	40.82% (40.71, 40.94)
≥65	88.70% (88.36, 89.04)	78.15% (77.80, 78.51)	60.10% (59.71, 60.48)
People with CMC	91.60% (91.34, 91.86)	80.87% (80.59, 81.14)	62.40% (62.10, 62.69)
Pregnant women	81.24% (80.55, 81.92)	69.47% (68.75, 70.19)	51.19% (50.42, 51.96)
Healthcare workers	7.28% (6.60, 7.95)	8.62% (7.95, 9.30)	2.05% (1.39, 2.70)

* Target population: healthcare personnel, persons who have chronic health conditions, all persons aged ≥ 65 years, all children from 6 months through 2 years of age, pregnant women

† % of cases that can be avoided = (attack rate of no vaccination - attack rate of vaccine policies) x 100 ÷ attack rate of no vaccination

Table 22 Proportion of deaths prevented for target population + children 2-5 years old vaccine policy , by different vaccine coverage

Population	% of deaths that can be avoided† (95%CI)		
	100% Coverage	75% Coverage	50% Coverage
Total population	79.27% (74.70, 83.83)	66.78% (61.97, 71.58)	50.57% (45.48, 55.66)
Age (years)			
<2	82.07% (51.02, 113.11)	71.43% (103.85, 39.01)	59.88% (26.04, 93.72)
2-5	89.73% (66.62, 112.84)	82.70% (58.86, 106.54)	60.18% (34.15, 86.21)
6-18	71.90% (60.55, 83.26)	58.74% (46.81, 70.66)	41.11% (28.47, 53.76)
19-65	77.02% (70.99, 83.05)	64.31% (57.97, 70.64)	48.08% (41.38, 54.78)
≥65	90.88% (80.79, 100.97)	78.43% (67.78, 89.07)	64.27% (53.22, 75.52)
People with CMC	92.22% (84.29, 100.14)	81.29% (72.97, 89.61)	65.16 (56.30, 74.03)
Pregnant women	87.57% (47.14, 127.99)	81.62% (40.14, 123.10)	60.00% (14.89, 105.11)
Healthcare workers	28.97% (-36.58, 94.53)	41.12% (-22.06, 104.30)	29.91% (-35.47, 95.28)

* Target population: healthcare personnel, persons who have chronic health conditions, all persons aged ≥ 65 years, all children from 6 months through 2 years of age, pregnant women

† % of deaths that can be avoided = (mortality rate of no vaccination - mortality rate of vaccine policies) x 100 ÷ mortality rate of no vaccination

Table 23 Proportion of cases prevented for target population + children 2-18 years old vaccine policy , by different vaccine coverage

Population	% of cases that can be avoided† (95%CI)		
	100% Coverage	75% Coverage	50% Coverage
Total population	99.37% (99.30, 99.44)	98.20% (98.13, 98.27)	92.88% (92.81, 92.96)
Age (years)			
<2	99.65% (99.19, 100.11)	98.83% (98.37, 99.30)	94.54% (94.06, 95.01)
2-5	99.76% (99.48, 100.05)	99.07% (98.78, 99.35)	95.05% (94.76, 95.34)
6-18	99.78% (99.65, 99.91)	99.09% (98.96, 99.22)	95.06% (94.93, 95.19)
19-65	99.10% (99.01, 99.19)	97.61% (97.52, 97.70)	91.41% (91.32, 91.51)
≥65	99.71% (99.39, 100.03)	98.89% (98.57, 99.21)	94.66% (94.33, 94.99)
People with CMC	99.78% (99.53, 100.03)	99.03% (98.78, 99.28)	94.94% (94.69, 95.20)
Pregnant women	99.50% (98.88, 100.13)	98.36% (97.73, 98.99)	93.10% (92.46, 93.75)
Healthcare workers	76.60% (75.98, 77.22)	59.72% (59.04, 60.40)	32.49% (31.78, 33.20)

* Target population: healthcare personnel, persons who have chronic health conditions, all persons aged ≥ 65 years, all children from 6 months through 2 years of age, pregnant women

† % of cases that can be avoided = (attack rate of no vaccination - attack rate of vaccine policies) x 100 ÷ attack rate of no vaccination

Table 24 Proportion of deaths prevented for target population + children 2-18 years old vaccine policy , by different vaccine coverage

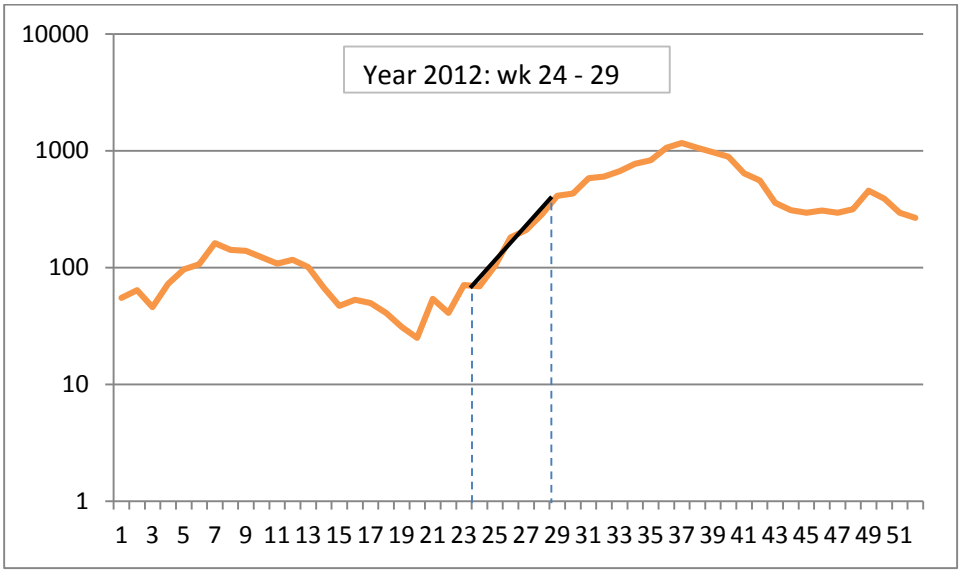
Population	% of deaths that can be avoided† (95%CI)		
	100% Coverage	75% Coverage	50% Coverage
Total population	99.47% (95.29, 103.64)	98.35% (94.15, 102.54)	93.83% (89.54, 98.11)
Age (years)			
<2	99.39% (70.72, 100.11)	96.96% (67.94, 125.98)	95.74% (66.55, 124.94)
2-5	99.82% (77.79, 121.85)	99.28% (77.19, 121.37)	95.32% (72.79, 117.84)
6-18	99.85% (89.81, 109.89)	98.95% (88.87, 109.03)	96.56% (86.36, 106.76)
19-65	99.26% (93.80, 104.72)	98.00% (92.51, 103.49)	92.52% (86.88, 98.16)
≥65	99.69% (90.02, 109.36)	98.86% (89.14, 108.57)	94.90% (85.00, 104.80)
People with CMC	99.67% (92.03, 107.32)	99.09% (91.42, 106.76)	94.99% (87.17, 102.82)
Pregnant women	98.92% (60.59, 137.25)	100.00% (61.87, 138.13)	92.97% (53.53, 132.41)
Healthcare workers	82.24% (27.85, 136.64)	68.22% (10.68, 125.77)	62.62% (3.86, 121.37)

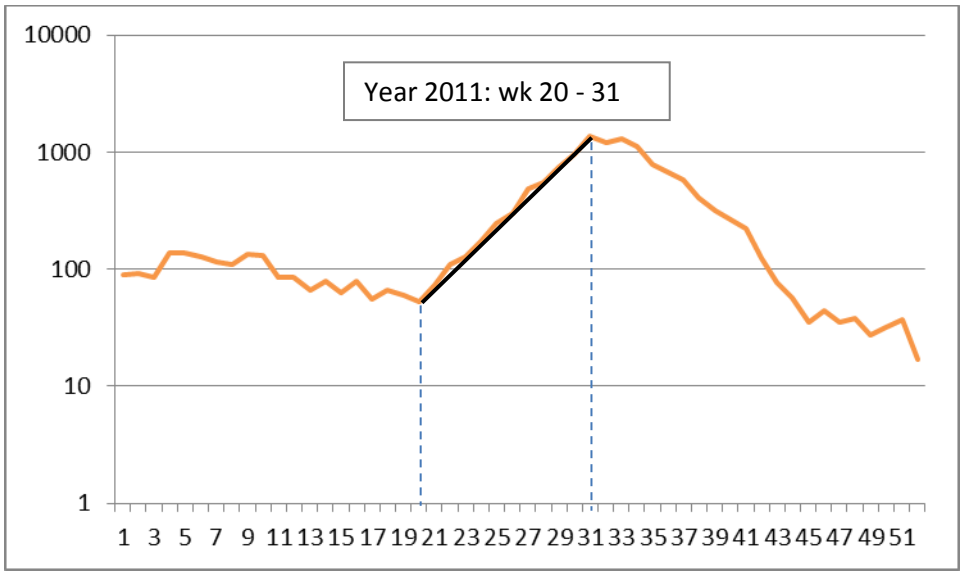
* Target population: healthcare personnel, persons who have chronic health conditions, all persons aged ≥ 65 years, all children from 6 months through 2 years of age, pregnant women

† % of deaths that can be avoided = (mortality rate of no vaccination - mortality rate of vaccine policies) x 100 ÷ mortality rate of no vaccination

APPENDIX C: SUPPLEMENTARY FIGURES

The numbers of influenza cases by week from 2003 to 2012 were obtained. An epidemic curve with logarithm scale for each year was plotted. Linear increase in cases on a logarithmic scale indicates exponential increase in the number of cases. The figure 14 presents 10 graphs of the analyzed years

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Year 2011: wk 20 - 31
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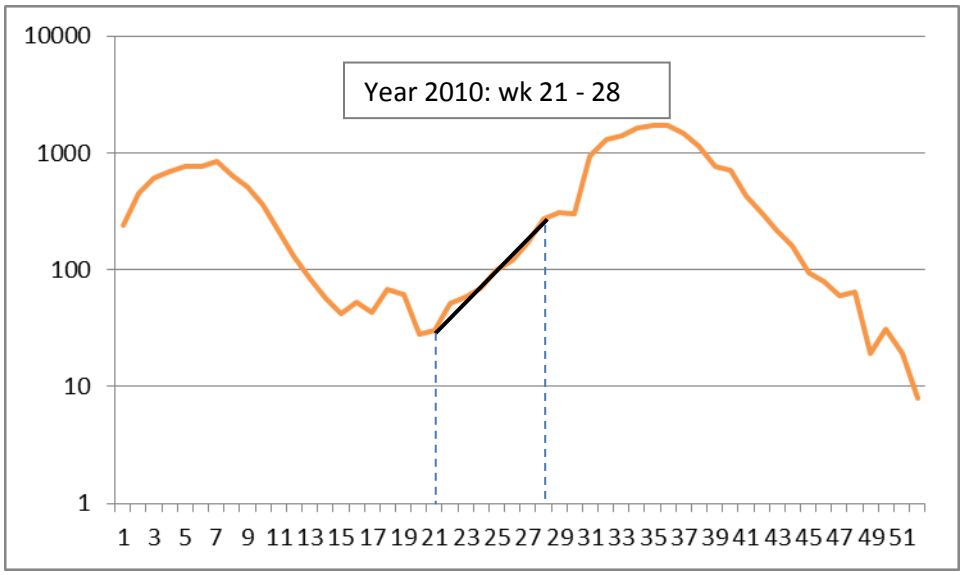
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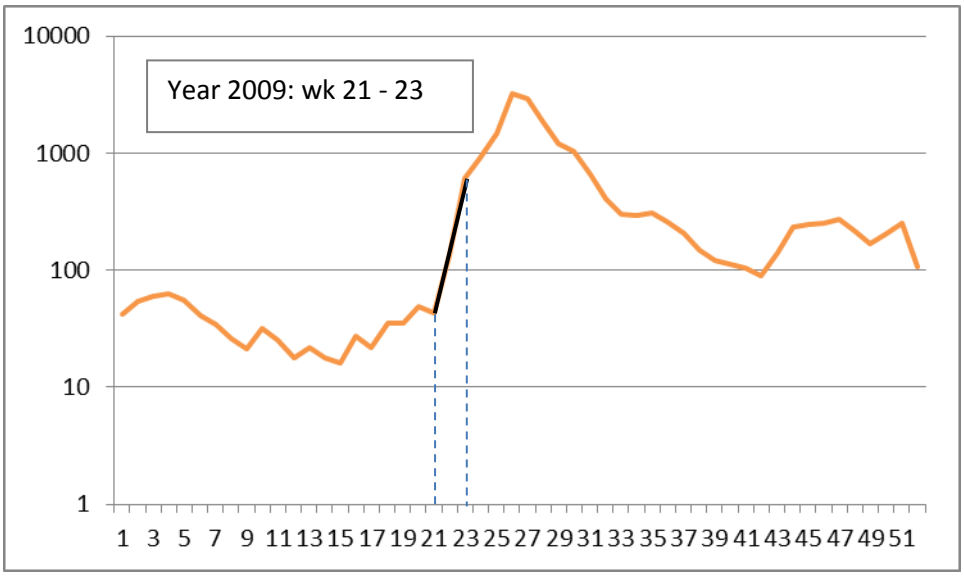
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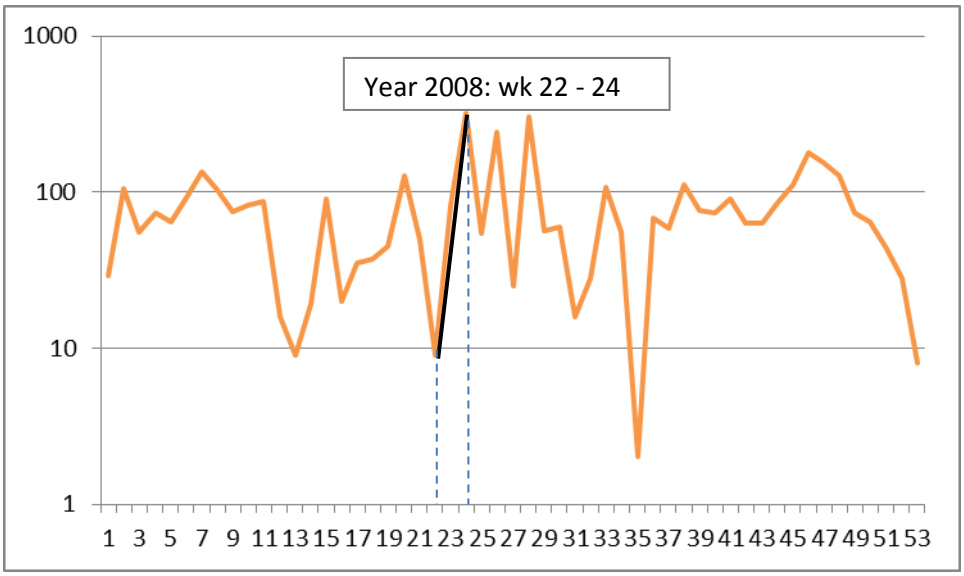
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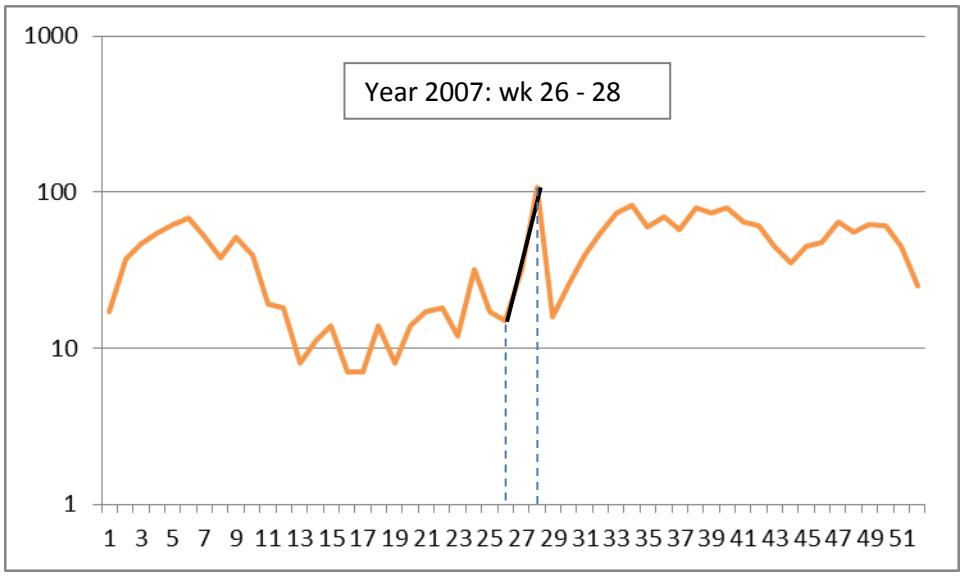
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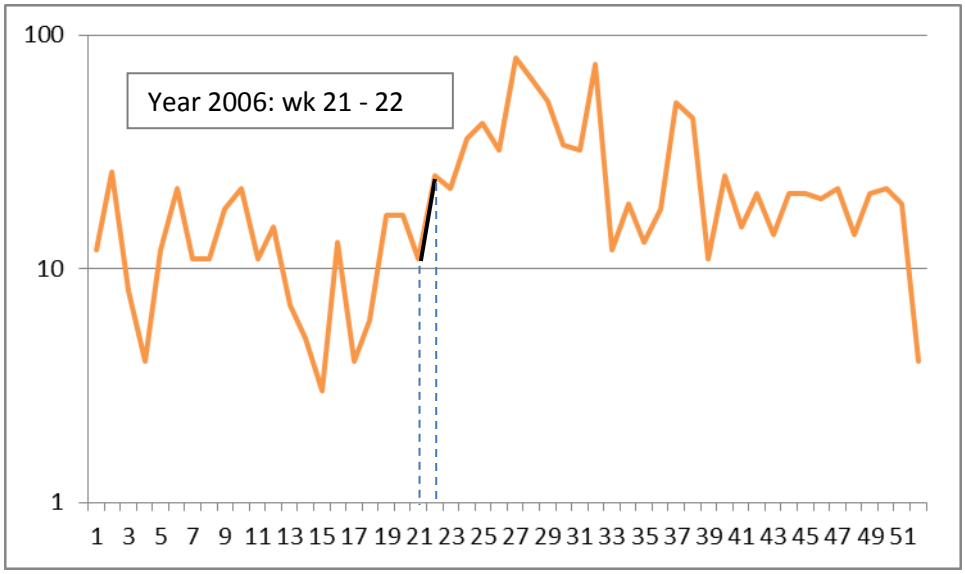
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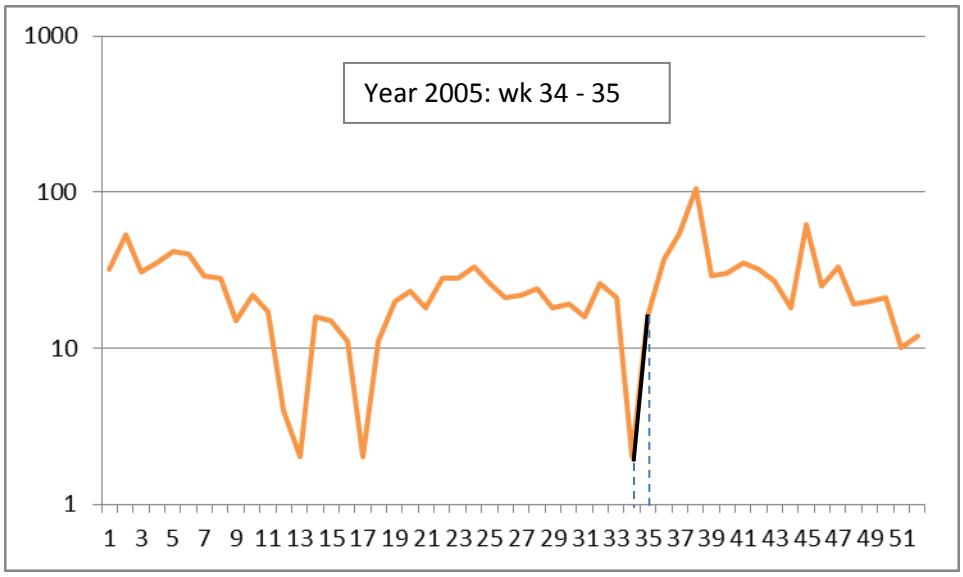
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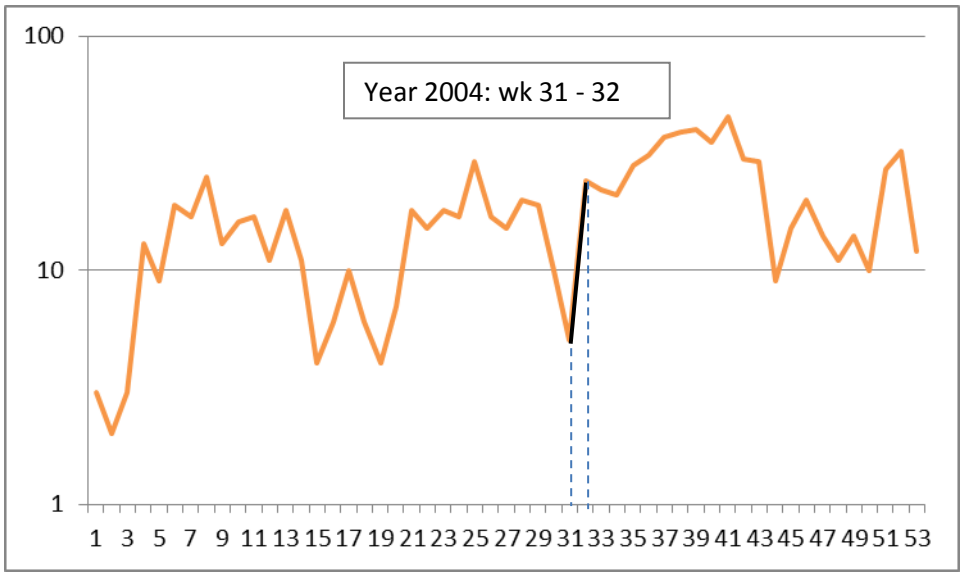
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Year 2004: wk 31 - 32
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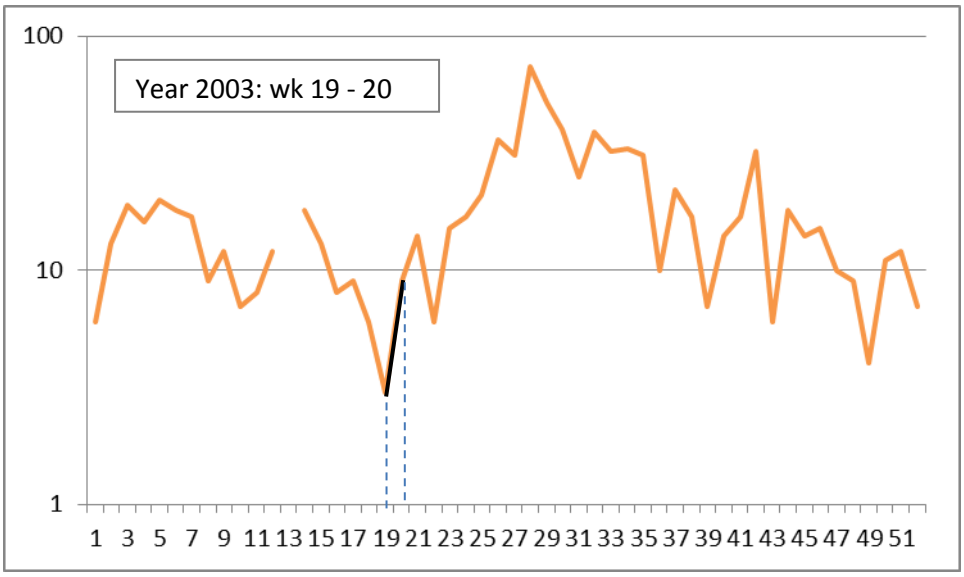

Figure 14 Number of reported influenza case in bangkok, 2003 - 2012

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